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ISONIAZID IN THE TREATMENT OF PULMONARY TUBERCULOSIS

SECOND REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS CHEMOTHERAPY TRIALS COMMITTEE*

In February, 1952, the Medical Research Council appointed their Tuberculosis Chemotherapy Trials Committee to plan a clinical trial of isonicotinic acid hydrazide (isoniazid) in pulmonary tuberculosis. Selected hospitals were invited to co-operate, and the first patient started treatment on March 29, 1952. The trial is still continuing and has expanded steadily. The number of participating hospitals now stands at 52, and more than 1,100 patients are undergoing, or have undergone, prescribed courses of treatment and observation.

The trial was designed so that monthly progress reports on each patient could be collected, and the accumulated information reviewed, from week to week. This continual review of results in a large number of patients has not only facilitated early publication of reports, but also enabled the Committee to stop the allocation of some treatments and to introduce others during the course of the trial.

The first report of the Committee was published on October 4, 1952 (Medical Research Council, 1952). It compared the value of isoniazid with that of streptomycin + P.A.S. in the treatment of pulmonary tuberculosis, in a series of 331 patients after three months' observation and treatment. The report suggested that over this period isoniazid lay within the same range of efficacy as streptomycin + P.A.S. It demonstrated, however, a frequent and rapid development of bacterial resistance to the drug and showed that this was a serious problem, since it affected the response to treatment.

The present report studies the effects of streptomycin combined with isoniazid ; it compares this treatment with those investigated in the first report—namely, streptomycin + P.A.S. and isoniazid alone. The progress of a total of 364 patients who were treated for three months is now presented. They were divided at random on entry to the trial into three series receiving one or another of the three treatments.

The list of the 40 hospitals which have contributed cases for this analysis, and the names of the co-operating clinicians, bacteriologists, and pathologists, are given at the end of the report. The bacteriologists and pathologists formed a laboratory subcommittee under the chairmanship of Professor R. Cruickshank. The trial was co-ordinated by Drs. Marc Daniels and Wallace Fox, of the Council's Tuberculosis Research Unit ; Dr. Fox and Dr. Ian Sutherland (of the Council's Statistical Research Unit) analysed the present results and prepared the report. *X*-ray assessments were made by Dr. L. G. Blair. The isoniazid used throughout the trial has been supplied as " nydrazid " by E. R. Squibb and Sons.

*Members of the Committee: Sir Geoffrey Marshall (chairman), Professor J. W. Crofton, Professor R. Cruickshank, Dr. Marc Daniels, Dr. J. E. Geddes, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. D. A. Mitchison, Dr. W. D. M. Paton, Dr. J. G. Scadding, Dr. Norman Smith, Dr. P. D'Arcy Hart (secretary).

I. PLAN AND CONDUCT OF THE TRIAL

The plan and conduct of the trial have already been described in the first report and some points are dealt with more fully there.

1. General

When a patient has been accepted for the trial, treatment is allocated by the Tuberculosis Research Unit from confidentially held prearranged lists based upon random sampling numbers.

After admission to the trial and a preliminary week of observation, all patients are kept under observation for six months. During the first three months the prescribed treatment is followed for every case. During the second three months Group 3 cases (see later description of groups) remain on the same treatment. For other cases the clinician is free to undertake any treatment he wishes.

At the end of the first, second, and third month of treatment, clinical progress reports for each patient on standard forms are sent to the Tuberculosis Research Unit. At six months the clinicians send a final progress report and a full case summary.

The information is scrutinized as soon as it is received, and the most important items from the clinical progress reports are entered on special cards. Information for each patient is thus accumulated, and with these cards regular analyses of results are carried out. Laboratory data are kept separately by the bacteriologists and pathologists, and are called in as required (see Section III of this report).

2. Type of Case

Before acceptance into the trial, basic requirements for all cases were laid down as follows :—At the start of treatment : (1) Tubercle bacilli must have been demonstrated: there must be either a positive direct smear from a sputum specimen taken within the previous two weeks, or a positive culture derived from a specimen taken not more than two months previously. (2) The tubercle bacilli must not, so far as is known, be streptomycin-resistant or P.A.S.-resistant. (3) The patient must not have had more than 15 g. streptomycin and/or 300 g. P.A.S. within the previous three months, and not more than 3 g. isoniazid at any time (this last requirement was added soon after the start of the trial). (4) The patient must not be undergoing pneumoperitoneum, nor have any form of collapse therapy for the lung requiring treatment. (For fuller criteria see the first report.)

Twelve cases (3%) did not conform entirely to the bacteriological requirements, but are nevertheless included in the clinical analysis. In none of these patients was the diagnosis in doubt, and for most of them it had been established bacteriologically either before or after starting treatment, though not within the stipulated period. These cases have, however, been excluded from the bacteriological analysis (see Section III).

Cases satisfying the above requirements were admitted to the trial in one of three main disease groups: (1) acute rapidly progressive pulmonary tuberculosis believed to be of recent origin; (2) other forms of pulmonary tuberculosis considered suitable for chemotherapy; (3) chronic forms of pulmonary tuberculosis expected to make only a limited response to streptomycin + P.A.S.

Under these three headings eight subgroups were defined as follows: (1A) Bilateral lesions; age 15–30. (The definition of this subgroup corresponds to that of cases admitted to the earlier chemotherapy trials, 1946–52.) (1B) Bilateral lesions; other ages. (1C) Predominantly unilateral lesions; all ages. (2A) Chronic cases with a recent exudative lesion. (2B) Primary tuberculosis with manifest recent lesions diagnosed not more than six months previously. (2C) Other forms. (3A) Patients who have previously had, in all, not more than 15 g. streptomycin and/or 300 g. P.A.S. and/or 3 g. isoniazid. (3B) Other patients who have had some chemotherapy, but not more than 15 g. streptomycin and/or 300 g. P.A.S. within the previous three months, and/or 3 g. isoniazid. It was realized that there would be some overlap between Groups 2 and 3, as well as between the subgroups of Group 2.

3. Intake of Cases

Group 1 cases are selected by a central panel of clinicians; cases in Groups 2 and 3 are, in the main, selected by the clinicians in the co-operating hospitals from the patients already under their care.

4. Treatment

The dosage of each drug used was as follows:—*Streptomycin* (not dihydrostreptomycin): 1 g. daily, in one intramuscular injection. (Children under 15: 15 mg. per kg. of body weight daily, up to a maximum of 1 g.) *P.A.S.*: 20 g. of the sodium salt daily, in four doses, by mouth. (Children under 15: 1 g. per 3 kg. of body weight daily, up to a maximum of 20 g.) *Isoniazid*: 200 mg. daily, in two doses of 100 mg. given 12-hourly, by mouth. (Children under 15: 3 mg. per kg. of body weight daily, up to a maximum of 200 mg.)

5. Evolution of the Trial

The large number of cases and the continual analysis of the results have enabled the Tuberculosis Chemotherapy Trials Committee to introduce new treatments and to stop allocating other treatments during the course of the trial, and so to study fresh problems in the application of isoniazid as they arose. The trial has thus proceeded in several stages. The time-table has been complicated by the fact that for several reasons the new treatments have not been introduced at the same time in each of the disease subgroups of the trial. Subgroup 1A and Group 3 have followed patterns different from those of the other groups. Fig. 1 illustrates this complex time-table, and the following paragraphs should be read in conjunction with this figure.

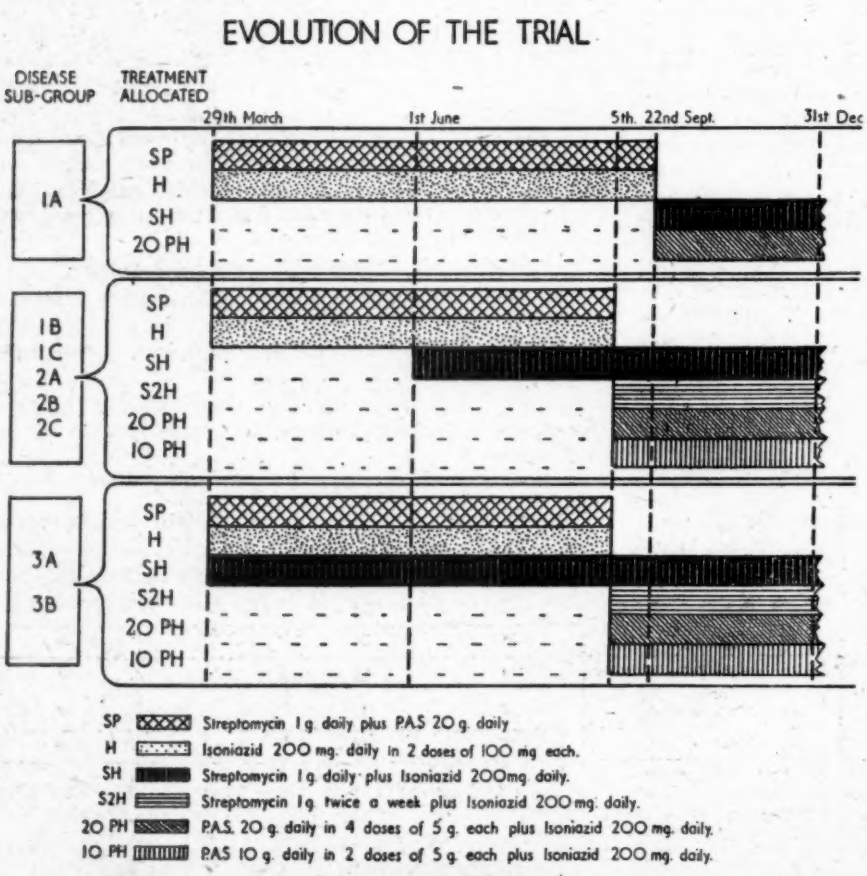

FIG. 1.—The treatments allocated in each disease subgroup from the start of the trial to the present time, showing the period of allocation of each treatment.

When the trial began on March 29, 1952, the first problem was to decide whether isoniazid was an effective drug when compared with the best chemotherapy known at that time—namely, streptomycin + P.A.S. Accordingly, two treatments—streptomycin + P.A.S. (SP) and isoniazid (H)—were allocated concurrently, and at random, to cases in all disease groups.

In view of the development of bacterial resistance to other antituberculosis drugs when given alone, it was decided from the outset to study also the results of combining isoniazid with another effective drug. A third treatment, streptomycin + isoniazid (SH), was therefore introduced at the start of the trial in Group 3, in which the cases (by definition) were expected to make only a limited response to streptomycin + P.A.S. In this way fundamental bacteriological information would become available as soon as possible.

As the trial proceeded there was growing evidence concerning the frequent development of bacterial resistance to isoniazid when given alone. The Committee therefore decided to introduce the SH treatment throughout the trial (except in subgroup 1A) from June 1, while continuing a concurrent allocation of cases to SP and H. Although the three treatments were allocated at random as

before, it was arranged, without the knowledge of the clinicians, that rather more patients should be admitted to the SH series than to either of the other two, because of its potential importance.

The cases in subgroup 1A (acute rapidly progressive tuberculosis of recent origin, bilateral and between the ages of 15 and 30) were of special importance since they corresponded by definition to those in all the previous Medical Research Council tuberculosis chemotherapy trials. The aim of the Committee was to have a sufficiently large number of cases in this subgroup to enable a clear-cut comparison to be made between isoniazid alone and each of the treatments allocated in the earlier trials. For this reason the two treatments SP and H were allocated in this subgroup from the start of the trial until September 22, by which date 99 cases had been admitted, and the Committee had decided from the bacteriological information then available that it was unjustifiable to continue to allocate isoniazid alone. From this date onwards, two other treatments were adopted for subgroup 1A—namely, SH and 20 PH (20 g. P.A.S. daily + isoniazid 200 mg. daily). (See Fig. 1.)

By the beginning of September, 1952, the numbers of patients who were on the SP and H treatments in other subgroups were adequate; also, the bacteriological analysis for the first report, although incomplete, suggested that isoniazid resistance was a serious problem affecting clinical progress. From September 5 onwards, therefore, the allocation of cases to SP and H was stopped throughout the trial (except, as stated above, in subgroup 1A). As it was essential to concentrate upon combined therapy with a view to the prevention of drug resistance, three new treatments were introduced in addition to SH (streptomycin 1 g. daily+ isoniazid 200 mg. daily)—namely, S2H (streptomycin 1 g. twice weekly + isoniazid 200 mg. daily), 20 PH (20 g. P.A.S. daily + isoniazid 200 mg. daily), and 10 PH (10 g. P.A.S. daily + isoniazid 200 mg. daily). The trial of these four treatments is still proceeding.

The first isoniazid report (Medical Research Council, 1952) compared the progress after three months' treatment of all the SP and H cases admitted to the trial before June 1, 1952. (During this period 38 Group 3 cases were allocated to the SH treatment; but, because this number of very chronic cases was considered to be inadequate for the assessment of clinical results, no comparison was then made with the Group 3 cases allocated concurrently to SP and H.)

The clinical section of the present report analyses the progress after three months' treatment of all the 364 cases which were admitted concurrently to the three treatments SP, H, and SH—that is, all the Group 3 cases allocated between March 29 and September 5, and all cases in the other disease groups (except subgroup 1A) allocated from June 1 until September 5 (see Fig. 1). The progress of the SH patients is compared with that of the SP and also of the H patients. Direct comparison between the SP and the H patients (numbering more than 500 since the start of the trial) is not made here, but will be the subject of a further report.

The bacteriological section of the present report analyses the tests for tubercle bacilli in the sputum and the development of drug resistance for the same group of 364 cases.

6. Total Number of Patients in the Present Analysis

Table I sets out the number of cases according to treatment, and shows that, of the 364 cases, 102 have been treated with streptomycin + P.A.S., 120 with isoniazid, and 142 with streptomycin + isoniazid. (Of the Group 3 cases, 29 SP and 40 H were included in the first report but appear again in the present analysis, since they were admitted concurrently with 38 SH patients. Subgroup 1A does not appear in the present analysis, since the SH treatment was not allocated concurrently with the SP and H treatments in this subgroup. Consequently, whereas Group 1 of the first report included cases in all three subgroups, Group 1 of the present report includes cases in 1B and 1C only.)

II. CLINICAL PROGRESS

1. Exclusions

Before detailing the clinical exclusions it should be pointed out that Table I and the clinical analysis include approximately 20 patients who were found to have had streptomycin- or P.A.S.-resistant organisms at the start of treatment, although this was not known when they entered the trial. Because their response to treatment may have been affected by this, it would have been desirable to exclude these cases from the clinical analysis. This has not been done because a few P.A.S. sensitivity tests are still pending. A subsidiary analysis has shown no evidence that the conclusions drawn below are in any way affected by the retention of these cases for the time being.

The totals in Table I do not include 39 cases which were admitted concurrently with the 364 but subsequently excluded for the following reasons:

(i) The 7 cases in Group 2B were excluded (3 SP, 2 H, and 2 SH). This group was too small and too different from the others to justify its retention.

(ii) Five cases were excluded before treatment was started:
1 patient died before admission to hospital (SH);
2 patients refused admission to hospital (1 SP, 1 H);
1 patient refused treatment (SP);
1 patient, although admitted, did not start treatment as no positive sputum could be obtained (H).

TABLE I.—*Number of Cases Treated Concurrently with SP, H, and SH*

		Treatment			All Cases
		Streptomycin Plus P.A.S.	Isoniazid	Streptomycin Plus Isoniazid	
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	1B. Bilateral; under 15 years and 31 or more	4	7	10	21
	1C. Unilateral; all ages	21	19	27	67
	Total	25	26	37	88
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	2A. Chronic with recent spread	14	13	24	51
	2C. Other forms (excluding primary disease)	24	31	32	87
	Total	38	44	56	138
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	3A. Very little previous chemotherapy	12	15	14	41
	3B. Some previous chemotherapy, but not recently	27	35	35	97
	Total	39	50	49	138
All cases		102	120	142	364

(iii) Twenty-seven cases were excluded after treatment had begun:

1 patient was found to have had four months' chemotherapy up to within a month of entering the trial (H);
1 patient was found to have a carcinoma of the bronchus, proved on biopsy (H);
3 patients were given the wrong treatment in error (2 SP, 1 SH), 2 having SP+H for one month, the third having SP+H for two months;
6 patients discharged themselves against medical advice (1 in the first month, 3 in the second, and 2 in the third) (4 SP, 1 SH, 1 H);
11 patients had severe toxic reactions attributed to streptomycin (6 SH, 5 SP);
2 patients had severe toxic reactions attributed to P.A.S. (2 SP);
1 patient was found to be pregnant and this was considered by the clinician in charge a contraindication to streptomycin (SH);
2 changes of treatment were necessary in the first month—namely, in 1 H case which showed gross spread radiologically and in which streptomycin was added because the patient was considered at risk of death in the absence of this treatment (the radiographic appearances remained unaltered in the next two months), and in another H case which deteriorated clinically but not radiographically and in which streptomycin+P.A.S. was added after four weeks.

It will be seen that there were 13 exclusions because of drug intolerance—11 to streptomycin (5 SP and 6 SH) and 2 to P.A.S. Although many patients intolerant to streptomycin or P.A.S. can be desensitized, these exclusions for drug intolerance must be considered a defect of therapy with streptomycin or with P.A.S. when compared with isoniazid, for in no case was there any interference with the prescribed regime of isoniazid due to toxicity, whether the isoniazid was taken alone or in combination. Against these 13 exclusions there is one exclusion representing a definite failure of isoniazid therapy, and one in which clinical deterioration was reported.

One patient whose treatment was changed from H to SH at the end of the second month has been included throughout as an H patient.

2. Toxicity

Toxicity of Streptomycin and of P.A.S.—Apart from the 13 cases referred to in the previous paragraph, in which treatment had to be stopped, there were some slighter toxic reactions to streptomycin in patients on the SP and SH treatments and to P.A.S. in patients on the SP treatment. These reactions were sometimes troublesome and worrying, but did not interfere unduly or more than temporarily with the prescribed regime of chemotherapy. Nevertheless, toxic reactions to streptomycin must be accepted as a defect of the combination streptomycin + isoniazid as of the combination streptomycin + P.A.S.

Toxicity of Isoniazid.—There have been no reports of serious toxicity from isoniazid in any of the trial patients, with the dosage used, over a period of three months, and there is nothing further to add, at this stage, to the information presented in the previous report.

3. Condition on Admission

Table II shows the condition of patients before the start of treatment as reflected by their general condition (assessment by the clinician in charge), temperature, sedimentation rate (Westergren 200 mm. reading at one hour), and the extent of cavitation on *x*-ray film (as estimated by an independent radiological assessor, unaware of the treatment of any case). It can be seen that, judging by the factors listed, the SP, H, and SH cases, both in Group 1 and in Group 3, have a reasonably similar distribution of severe and less severe illness. In Group 2, however, the SP patients appear to have been on the average rather more ill than the SH and H patients. For the totals of all groups the three treatment series are comparable.

4. Results at the End of Three Months

In the following sections, after a general note on the low mortality, a comparison is made between the progress of the patients on streptomycin + isoniazid (SH) and that of patients on streptomycin + P.A.S. (SP). This is followed by a comparison of the progress of patients on streptomycin + isoniazid (SH) and the progress on isoniazid (H) alone.

Mortality.—There were four deaths among the 364 cases (1.1%) during the three months of treatment; two in 102 SP patients, one in 120 H patients, one in 142 SH patients. One SP patient (in Group 3A), who died 14 days after the start of treatment, suffered clinically from chronic bronchitis and emphysema, and cannot be regarded as having died from tuberculosis; the H patient (in Group 2C) died from

TABLE II.—*Condition on Admission of SP, H, and SH Cases*

	Treatment	Total	General Condition			Average Evening Temperature in Pre-treatment Week*				Sedimentation Rate (Westergren 200 mm. Reading at 1 Hour)				Extent of Cavitation†			
			Good	Fair	Poor	Afebrile	Under 99°F.	99–99·9° F.	100° F. or more	0–10	11–20	21–50	51 or more	Nil	1-plus	2-plus	3-plus
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25 100	3 12	11 44	11 44	6 24	7 28	7 28	5 20	2 8	0 0	8 32	15 60	3 12	11 44	8 32	3 12
	H	26 100	6 23	10 38	10 38	8 31	8 31	9 35	1 4	1 4	1 4	10 38	14 54	7 27	7 27	5 19	7 27
	SH	37 100	4 11	20 54	13 35	5 14	13 35	13 35	6 16	0 0	5 14	18 49	14 38	5 14	16 43	14 38	2 5
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	38 100	7 18	17 45	14 37	10 26	14 37	6 16	8 21	3 8	7 18	13 34	15 39	10 26	9 24	9 24	10 26
	H	44 100	16 36	17 39	11 25	24 55	11 25	6 14	3 7	7 16	10 23	17 39	10 23	17 39	11 25	13 30	3 7
	SH	56 100	18 32	31 55	7 12	24 43	19 34	9 16	4 7	8 14	12 21	24 43	12 21	19 34	17 30	16 29	4 7
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	39 100	13 33	14 36	12 31	21 54	15 38	3 8	0 0	6 15	10 26	14 36	9 23	6 15	6 15	17 44	10 26
	H	50 100	10 20	26 52	14 28	28 56	17 34	3 6	2 4	3 6	13 26	21 42	13 26	5 10	6 12	19 38	20 40
	SH	49 100	16 33	19 39	14 29	24 49	13 27	9 18	3 6	11 22	4 8	21 43	13 27	5 10	8 16	16 33	20 41
All cases	SP	102 100	23 23	42 41	37 36	37 36	36 35	16 16	13 13	11 11	17 17	35 34	39 38	19 19	26 25	34 33	23 23
	H	120 100	32 27	53 44	35 29	60 50	36 30	18 15	6 5	11 9	24 20	48 40	37 31	29 24	24 20	37 31	30 25
	SH	142 100	38 27	70 49	34 24	53 37	45 32	31 22	13 9	19 13	21 15	63 44	39 27	29 20	41 29	46 32	26 18

* A patient was considered afebrile if *every* evening temperature in the pre-treatment week of observation was below 99° F. (37·2° C.).
† Assessment on a single film taken before treatment started. Tomograms were not taken into account.

congestive cardiac failure the day after starting treatment. These two cases do not represent a failure of treatment, in contrast to the other two patients—one on SP, the other on SH (from Groups 3A and 3B)—who died of their tuberculous disease 32 days and 22 days respectively after the start of treatment;* both were very ill on admission to the trial.

5. The Comparison between SH (Streptomycin + Isoniazid) and SP (Streptomycin + P.A.S.)

General Condition.—Change in the clinical condition was assessed by the physician in charge of the patient. It represents an overall impression of the patient's progress, being based on the clinical observations, the patient's appearance, and his feeling of well-being (or lack of it). Table III shows that on each treatment a considerable percentage of patients improved—87% of 142 SH patients and 75% of 102 SP patients. This difference just attains statistical significance at the 5% level, due mainly to the experience in Group 3. In this group of very chronic cases, 51% of 39 SP patients showed 1-plus (moderate) improvement, and none had 2-plus (considerable) improvement; in the 49 SH patients the corresponding figures are 49% and 22%. In Group 1, the acute rapidly progressive disease, all the 25 SP patients and 36 of the 37 SH patients improved clinically.

Weight Changes.—The weight changes for the three-months period are set out in Table IV, and here the SH patients have benefited strikingly compared with the SP patients. The difference in the average weight gains for the totals (6.1 lb. and 13.0 lb.—2.8 and 5.9 kg.), and also that for each disease group, is statistically highly significant. Of the 136 SH patients, 82% gained 7 lb. (3.2 kg.) or more and 42% gained 1 stone (6.3 kg.) or more. The corresponding figures for the 97 SP patients are 45% and 13%. It is noteworthy that the acute (Group 1) cases on both treatments have fared better than the less acute cases, and that in this group, too, the SH patients have benefited more than the SP patients. Of 36 SH patients 61% have gained 1 stone or more, compared with 32% of 25 SP patients. Of

TABLE III.—*General Condition at the End of the Third Month Compared with General Condition on Admission*

	Treatment	Total	Improvement		No Change	Deterioration		Death
			2-plus	1-plus		1-minus	2-minus	
		No. %	No. %	No. %	No. %	No. %	No. %	No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25 100	12 48	13 52	0 0	0 0	0 0	0 0
	H	26 100	13 50	10 38	3 12	0 0	0 0	0 0
	SH	37 101	18 49	18 49	1 3	0 0	0 0	0 0
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	38 101	12 32	19 50	6 16	0 0	1 3	0 0
	H	44 99	12 27	27 61	3 7	1* 2	0 0	1 2
	SH	56 99	21 37	31 55	4 7	0 0	0 0	0 0
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	39 100	0 0	20 51	16 41	1 3	0 0	2 5
	H	50 100	7 14	25 50	15 30	2 4	1 2	0 0
	SH	49 100	11 22	24 49	13 27	0 0	0 0	1 2
All cases	SP	102 101	24 24	52 51	22 22	1 1	1 1	2 2
	H	120 101	32 27	62 52	21 18	3* 2	1 1	1 1
	SH	142 100	50 35	73 51	18 13	0 0	0 0	1 1

* One patient changed treatment from H to SH at the end of two months, and is included here.

TABLE IV.—*Weight Changes in the First Three Months.*

	Treatment	Total Weighed	Weight Gain				No Change	Weight Loss		Average Gain in Weight per Patient (lb.)
			21 lb. or More	14–20 lb.	7–13 lb.	Less than 7 lb.		Less than 7 lb.	7 lb. or More	
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25 100	2 8	6 24	11 44	3 12	1 4	2 8	0 0	10·2
	H	26 101	9 35	8 31	6 23	2 8	1 4	0 0	0 0	17·3
	SH	36 101	14 39	8 22	11 31	2 6	0 0	1 3	0 0	16·6
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	36 100	1 3	3 8	11 31	9 25	3 8	7 19	2 6	4·9
	H	43 100	10 23	17 40	11 26	4 9	0 0	0 0	1‡ 2	15·6
	SH	54 101	9 17	14 26	23 43	6 11	1 2	1 2	0 0	13·1
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	36 102	1 3	0 0	9 25	20 56	2 6	2 6	2 6	4·6
	H	50 100	0 0	12 24	17 34	16 32	1 2	3* 6	1† 2	8·1
	SH	46 100	4 9	8 17	21 46	11 24	0 0	1 2	1 2	10·2
All cases	SP	97* 99	4 4	9 9	31 32	32 33	6 6	11 11	4 4	6·1
	H	119* 101	19 16	37 31	34 29	22 18	2 2	3 3	2‡‡ 2	12·8
	SH	136* 100	27 20	30 22	55 40	19 14	1 1	3 2	1 1	13·0

* For three other SP patients and five SH patients the weight changes are not available. Also two SP patients, one H patient, and one SH patient had died.
† One patient included here lost 11½ lb. in two months, was too ill to be weighed at three months, and died the following day.
‡ One patient changed treatment from H to SH at the end of two months, and is included here.

the total of 61 acute cases on SP or SH, only 4 (7%) have failed to gain some weight.

Temperature.—In the present analysis a patient was considered to be initially afebrile if the evening temperature was below 99° F. (37.2° C.) on *every day* of the week of preliminary observation. The same definition applied to the last week of the third month of treatment. Table V sets out the number of patients who were febrile in the pre-treatment week, but afebrile at three months. The patients are grouped according to the initial level of pyrexia. In a total of 88 febrile SH patients, 82% were afebrile at three months, compared with 76% of 63 SP patients. There is also little difference between the three disease groups; the figures for Group 1, the acute cases, were 81% of 32 SH patients and 84% of 19 SP patients. In none of these comparisons is there a statistically significant difference.

Of 53 SH patients who were afebrile in the pre-treatment week (not shown in the table) 6, or 11%, had a low-grade pyrexia at three months (an occasional evening temperature above 99° F.). The corresponding figures for the SP patients were 4 out of 37, also 11%.

Sedimentation Rate.—Table VI sets out the number of patients with an initially elevated blood sedimentation rate (B.S.R., Westergren) which was lowered after three months' treatment. Of 101 SH patients with an initial B.S.R. of 21 or more, 45% fell to normal (10 or less) in three months; the corresponding figure for 73 SP patients was only 21%. This difference is statistically highly significant. When the initial B.S.R. was 51 or more the rates were normal at three months in 18% of 39 SH patients, and in only 5% of 38 SP patients. The B.S.R. rose from an initially normal level in 4 of 19 SH cases and 3 of 10 SP cases (not shown in the table).

Radiographic Changes in First Three Months.—Table VII sets out the radiographic changes at the end of three months' treatment. The assessments were made by an independent reading of full-plate chest *x*-ray films by a radiologist unaware of the treatment in any case. (Since the radiographic reading was intended as a comparative measure of *x*-ray change and not as an absolute assessment, it was considered that the readings of a single radiologist could be fairly accepted for assessing the relative merits of

TABLE V.—*Number of Cases Febrile in the Pre-treatment Week who were Afebrile at the End of the Third Month*

	Treatment	Average Evening Temperature in the Pre-treatment Week						All Cases Febrile in the Pre-treatment Week	
		Under 99° F.		99° F.–99·9° F.		100° F. or More			
		Total	No. Afebrile at Three Months	Total	No. Afebrile at Three Months	Total	No. Afebrile at Three Months	Total	Afebrile at Three Months
									No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	7	5	7	7	5	4	19	16 *84*
	H	8	7	9	5	1	1	18	13 *72*
	SH	13	12	13	12	6	2	32	26 *81*
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	14	12	6	4	8	3	28	19 *68*
	H	11	9	5	4	3	3	19	16 *84*
	SH	19	16	9	6	4	2	32	24 *75*
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	14	11	2	2	0	0	16	13 *81*
	H	17	10	3	1	2	0	22	11 *50*
	SH	13	12	8	8	3	2	24	22 *92*
			No. %		No. %		No. %		
All cases	SP	35	28 *80*	15	13 *87*	13	7 *54*	63*	48 *76*
	H	36	26 *72*	17	10 *59*	6	4 *67*	59*	40 *68*
	SH	45	40 *89*	30	26 *87*	13	6 *46*	88*	72 *82*

* Two SP patients, one H patient, and one SH patient who died are excluded from this table.

TABLE VI.—*Number of Cases with a Raised Sedimentation Rate in the Pre-treatment Week whose Sedimentation Rate was Normal at the End of the Third Month*

	Treatment	Sedimentation Rate in the Pre-treatment Week						All Cases with Initial Sedimentation Rate of 21 or More	
		11–20		21–50		51 or More			
		Total	No. with B.S.R. 0–10 at 3 Months	Total	No. with B.S.R. 0–10 at 3 Months	Total	No. with B.S.R. 0–10 at 3 Months	Total	B.S.R. of 0–10 at 3 Months
									No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	0	0	8	3	15	0	23	3 *13*
	H	1	1	10	4	14	4	24	8 *33*
	SH	5	5	18	14	14	2	32	16 *50*
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	7	4	13	8	15	2	28	10 *36*
	H	9	5	17	4	10	3	27	7 *26*
	SH	12	8	24	17	12	3	36	20 *56*
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	10	7	14	2	8	0	22	2 *9*
	H	13	6	21	6	12	0	33	6 *18*
	SH	4	2	20	7	13	2	33	9 *27*
			No. %		No. %		No. %		
All cases	SP	17	11 *65*	35	13 *37*	38	2 *5*	73*	15 *21*
	H	23	12 *52*	48	14 *29*	36	7 *19*	84*	21 *25*
	SH	21	15 *71*	62	38 *61*	39	7 *18*	101*	45 *45*

* For two other H patients the sedimentation rates at three months are not available. Also one SP and one SH patient had died.

TABLE VII.—*Changes in Radiographic Appearances in First Three Months*

	Treatment	Total		Improvement						No Change		Deterioration						Death	
				3-plus		2-plus		1-plus				1-minus		2-minus		3-minus			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25	100	2	8	10	40	6	24	7	28	0	0	0	0	0	0	0	0
	H	26	101	2	8	8	31	8	31	5	19	1	4	2	8	0	0	0	0
	SH	37	100	9	24	12	32	10	27	5	14	1	3	0	0	0	0	0	0
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	38	101	4	11	10	26	14	37	9	24	0	0	0	0	1	3	0	0
	H	44	101	3	7	10	23	17	39	10	23	2	5	1†	2	0	0	1	2
	SH	56	100	8	14	20	36	11	20	17	30	0	0	0	0	0	0	0	0
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	39	100	1	3	5	13	13	33	18	46	0	0	0	0	0	0	2	5
	H	50	100	0	0	4	8	13	26	28	56	4	8	0	0	1*	2	0	0
	SH	49	100	1	2	4	8	16	33	25	51	2	4	0	0	0	0	1	2
All cases	SP	102	100	7	7	25	25	33	32	34	33	0	0	0	0	1	1	2	2
	H	120	100	5	4	22	18	38	32	43	36	7	6	3†	2	1*	1	1	1
	SH	142	100	18	13	36	25	37	26	47	33	3	2	0	0	0	0	1	1

* This patient had 2-minus deterioration at two months, was too ill to be *x*-rayed at three months, and died the following day.
† One patient included here had 2-minus deterioration at two months, changed treatment from H to SH, and still had 2-minus deterioration at 3 months.

different treatments.) In assessing improvement or deterioration three degrees were allowed—namely: 1-plus, 2-plus, and 3-plus, and 1-minus, 2-minus, and 3-minus. In total, the SH and SP groups both contain 64% who showed radiographic improvement. The improvement was more than 1-plus in 38% of SH patients and in 31% of SP patients. (In Group 1, the acute group, 2-plus or 3-plus improvement was seen in 57% of SH cases and 48% of SP cases.) In all there was radiographic deterioration in 3 patients, and one death on streptomycin + isoniazid, and one deterioration and two deaths of patients on streptomycin + P.A.S. The differences between the two treatments are not statistically significant.

Summary of the Comparison of SH and SP

In general condition the SH patients fared rather better than the SP patients, but only among the chronic cases was the difference more than very slight. It must be remembered that assessment of general condition is to a considerable extent influenced by a knowledge of all the other observations of the patient's progress, such as the B.S.R., weight changes, and temperature. The weight gains in all three disease groups were strikingly better for patients on the SH treatment than on the SP treatment. The SH combination also proved much the more effective in lowering the B.S.R. On the other hand, the two treatments had very similar effects on the temperature, and, most important, there were no significant differences in the radiographic response.

6. The Comparison between SH (Streptomycin + Isoniazid) and H (Isoniazid)

General Condition.—Comparing streptomycin + isoniazid with isoniazid alone, it was found in regard to general condition that the response of the patients to each treatment was very similar. Table III shows that 87% of the SH patients improved, compared with 78% of the H patients. Again the response of Group 1 cases is particularly satisfactory.

Weight Changes.—Table IV shows that the average gain in weight for 136 SH patients was 13.0 lb. compared with an average gain of 12.8 lb. for 119 H patients. In each of the three disease groups the two treatments show little difference. The very chronic cases (Group 3) have, however, fared less well on either treatment than the other two groups. The close similarity in weight gain of the SH and H patients indicates that the important factor in these striking increases is either the presence of isoniazid or the absence of P.A.S.

Temperature.—Of 88 pyrexial SH patients 82% became apyrexial, compared with 68% of 59 H patients (Table V). The greatest disparity is in the very chronic cases of Group 3, where the difference attains statistical significance. In the other groups it is not important.

Sedimentation Rate.—The SH treatment has proved more effective than isoniazid alone in lowering the B.S.R. (Table VI). In 101 SH patients with an initial B.S.R. of 21 or more there was a fall to normal (10 or less) in 45%. For 84 H patients the figure was only 25%, giving a statistically highly significant difference. The difference is apparent in all three disease groups.

Radiographic Changes in First Three Months.—Table VII shows that of 142 SH patients 64% improved radiographically, compared with 54% of 120 H patients. Moreover, 38% of the SH patients showed 2-plus or 3-plus improvement, compared with 22% of the H patients. This superiority of the SH treatment, which is apparent over the whole range of the *x*-ray assessment, is statistically highly significant. Taking the acute Group 1 alone, 57% of the SH patients showed 2-plus or 3-plus improvement, compared with 38% of the H patients. In total, 3 SH patients deteriorated radiographically and one died, compared with 11 deteriorations and one death on H alone. (All 3 SH deteriorations and 7 of the H deteriorations were slight.) The SH treatment has thus shown itself to be more effective radiographically than isoniazid alone.

Summary of the Comparison of SH and H

The SH treatment was more effective than H in lowering the blood sedimentation rate and also in improving the radiographic appearances, and was slightly more effective in lowering the temperature of pyrexial patients. The two treatments were very similar in their effect on the general clinical condition and on weight, both producing striking improvement.

III. BACTERIOLOGY

The Laboratory Subcommittee (chairman, Professor R. Cruickshank) has been responsible for prescribing uniform laboratory techniques and procedures for the centres. A detailed description and discussion of these procedures will be published later as part of a further report.

The first report on the trial (Medical Research Council, 1952) gave as much bacteriological information as was then available on the presence of tubercle bacilli in the sputum during treatment with streptomycin+P.A.S. and with isoniazid. An analysis of isoniazid-sensitivity tests at one, two, and three months demonstrated that isoniazid resistance developed frequently and rapidly; this resistance was shown to affect clinical progress.

The present section analyses the bacteriology of cases treated, concurrently, with streptomycin+isoniazid (SH), streptomycin+P.A.S. (SP), or isoniazid alone (H). These are the same patients as those reported on clinically in Section II. The bacterial content of the sputum of the patients is compared after one, two, and three months of treatment. The development of bacterial resistance to streptomycin is studied for the patients treated with SH and with SP, and the development of resistance to isoniazid in patients treated with SH and with H. Because of the time needed to obtain results of cultures from sputum specimens and to complete drug-sensitivity tests on those cultures, the present analysis omits results pending at two and three months for a small percentage of cases.

1. Exclusions

For the clinical section of this report, it was decided to retain in the analysis only those patients who completed three months' treatment or who died after starting treatment. The procedure adopted for this bacteriological section has been different from that for the clinical section; the results of all available complete tests at one, two, and three months have been used. Thus any complete tests from the small number of patients withdrawn from the clinical analysis have been included—provided they had been treated for at least one month.

On the other hand, 16 patients whose clinical progress is reported have been excluded entirely from the bacteriological analysis. It was laid down that all cases at the start of treatment must be bacteriologically positive for tubercle bacilli (see p. 521). For 12 cases (4 SP, 4 H, 4 SH) the records show that no tubercle bacilli had in fact been seen or isolated from pre-treatment specimens, although positive results were obtained subsequently on one or more occasions from 4 of them. All 12 have been excluded from the bacteriological tables. It should be emphasized that there was no doubt of the clinical diagnosis, and in fact for most of these cases a positive bacteriological test had been obtained, though not within the prescribed pre-treatment period.

Four other cases (2 SP, 2 SH), all from one small centre, have been excluded because the recording of the bacteriological information was manifestly unsatisfactory.

2. Bacterial Content of Sputum

Sputum collected during the pre-treatment week, and subsequently at monthly intervals, or more often, was examined by direct microscopy and by culture. Where there was no sputum, material from laryngeal swab or gastric lavage was cultured.

The procedure for taking specimens varied considerably from centre to centre. Many centres adhered simply to the minimum requirements for the trial—namely, a single specimen taken each month; in others, specimens were taken much more often. There was evidence that in some centres examinations were made more frequently for patients on some treatments than on others.

In analysing this varied material two important points had to be observed. One was to assess the results as nearly as possible *at* one, two, or three months after the start of treatment. The other was to ensure that no apparent advantage or disadvantage accrued to a particular treatment merely because numerous or few examinations had been made on those patients allocated to it.

To meet these requirements it was decided to assess the presence or absence of tubercle bacilli each month from the results of single complete examinations of specimens, one from each patient, collected on a date as near as possible to, or exactly at, one, two, and three months after the start of treatment. A test was regarded as incomplete, and was ignored, unless a culture result was available. No result was included for a given month if the date of collection of the nearest specimen examined lay more than 7 days on either side of the appropriate date. Where there was more than one complete test within this period of 15 days, that on or nearest to the appropriate date was chosen, to avoid bias. Table VIII of the present report is therefore not comparable with Table VIII of the first report, in which the "most positive" of the results obtained at any time *during* each month was recorded.

TABLE VIII.—*Presence of Tubercle Bacilli at Single Examinations made at Monthly Intervals*

	Treatment	Total Patients Examined		"Positive" Direct Examination†		"Scanty Positive" Direct Examination*†		Direct Examination Negative and Culture Positive; or Laryngeal Swab Positive		Direct Examination and Culture Negative; or Laryngeal Swab Negative	
		No.	%	No.	%	No.	%	No.	%	No.	%
At 1 month	SP	91	*99*	33	*36*	14	*15*	14	*15*	30	*33*
	H	107	*100*	37	*35*	20	*19*	26	*24*	24	*22*
	SH	131	*99*	39	*30*	23	*18*	27	*21*	42	*32*
At 2 months	SP	89	*100*	21	*24*	8	*9*	16	*18*	44	*49*
	H	110	*99*	28	*25*	20	*18*	30	*27*	32	*29*
	SH	132	*100*	17	*13*	22	*17*	27	*20*	66	*50*
At 3 months	SP	83	*100*	16	*19*	8	*10*	13	*16*	46	*55*
	H	101	*101*	30	*30*	11	*11*	23	*23*	37	*37*
	SH	117	*100*	10	*9*	11	*9*	18	*15*	78	*67*
By disease group at 3 months:											
Group 1	SP	21	*100*	3		2		4		12	*57*
	H	21	*100*	5		2		3		11	*52*
	SH	30	*100*	1		4		4		21	*70*
Group 2	SP	29	*100*	4		2		5		18	*62*
	H	35	*100*	8		6		5		16	*46*
	SH	43	*100*	2		2		8		31	*72*
Group 3	SP	33	*100*	9		4		4		16	*48*
	H	45	*100*	17		3		15		10	*22*
	SH	44	*100*	7		5		6		26	*59*

All patients were bacteriologically positive before treatment—that is, at least one pre-treatment specimen showed bacilli on direct examination or was positive on culture.

* Defined as follows: only a few clumps of acid-fast bacilli found after five minutes' search.

† Whether culture-positive or negative.

The results at one, two, and three months of the selected single examinations of the sputum for tubercle bacilli are set out in Table VIII. It will be clear from the foregoing paragraphs that, in all the bacteriological tables, each item represents a number of *patients* for each of whom a single test has been selected (by the method already stated), and not a total of all the *tests* performed on a smaller number of patients.

The recording of the pre-treatment findings was incomplete and biased, since it favoured positive results. For this reason no comparison is possible with the findings during treatment. The pre-treatment findings have, however, been used to check that the degree of positivity of the three treatment series was comparable at the start of treatment.

For the analysis of data at two and three months results have been included only for the specimens in which at least an eight-week period had elapsed since they were collected (this being the period recommended for the incubation of cultures before regarding them as negative). The results at the second and third months would otherwise have been unduly weighted by "positives," since specimens negative on direct examination and with no culture yet available would *not* have been included, while specimens directly positive, or with early positive cultures, *would* have been included.

Results

It will be seen from Table VIII that at the end of one month's treatment the results of the tests were negative both on direct examination and on culture in 33% of 91 SP cases, 22% of 107 H cases, and 32% of 131 SH cases. These differences are not statistically significant.

At the end of the second month the percentages of cases negative both on direct examination and on culture were 49% of 89 SP cases, 29% of 110 H cases, and 50% of 132 SH cases. It will be noted that the percentage had increased under each treatment from one to two months. Further, a definite superiority of the SH and SP treatments over the H treatment had appeared; the benefit to the SH and SP cases when compared with the H cases is highly significant statistically. There is no significant difference between the SH and SP series.

At three months, further increases in the percentages negative both on direct examination and on culture had occurred, the figures being 55% of 83 SP cases, 37% of 101 H cases, and 67% of 117 SH cases; there was by then a tendency for the SH cases to show a benefit over the SP cases, but the difference does not attain significance. The cases on H lagged well behind, the benefit to the SH cases being highly significant. It must again be emphasized that this table presents only findings of single tests and so is not necessarily indicative of "sputum conversion." At the other end of the scale the percentages with a positive direct examination at three months were 19% for the SP cases, 30% for the H cases, and 9% for the SH cases.

3. Sensitivity Tests

Strains isolated from specimens collected before starting treatment, and subsequently at least once a month, were tested for streptomycin sensitivity in the SP and SH patients and for isoniazid sensitivity in the H and SH patients. The technique employed for streptomycin sensitivity was similar to that in previous trials (Medical Research Council, 1948); that for isoniazid sensitivity is outlined later (p. 530).

In addition, as the importance of initial P.A.S. resistance in patients admitted to the SP treatment became apparent, it was laid down that a P.A.S.-sensitivity test should be performed on the earliest culture available (whenever possible from the pre-treatment specimen) for all patients from whom a history of one month or more of treatment with P.A.S. alone was obtained. These tests of P.A.S. sensitivity were performed in two laboratories (see Acknowledgments).

As with the recording of the sputum tests, a sensitivity test for a given month was accepted only if it was performed on a specimen collected not more than seven days before or after the appropriate date. When more than one such result was available the one referring to a specimen taken on or nearest to the appropriate date was selected.

4. Streptomycin Sensitivity

All tests in which the "resistance ratio"* is 8 or more are classed as resistant, provided the test organisms grew in 0.5 unit per ml. or more; this latter proviso has been introduced to make allowance for the occasional exceptionally low reading for the standard strain H37Rv (inhibition by 0.06 unit per ml.). Check-tests in the reference laboratory for these few test strains indicated that they were sensitive.

As already stated (p. 521), it was required that at the start of treatment the tubercle bacilli must not, so far as was known, be either streptomycin-resistant or P.A.S.-resistant, the object of this requirement being that if the case was allocated to the SP treatment the effectiveness of chemotherapy should not be hindered by pre-existent resistance to either drug, or, if allocated to the SH treatment, by pre-existent resistance to streptomycin. In fact, for many cases the drug sensitivity was not known until well after the start of treatment, when the results of pre-treatment sensitivity tests had become available. It was then found that in 9 patients (2 SP, 7 SH) the bacilli had been streptomycin-resistant initially. Of these, 7 had a history of treatment with streptomycin, alone or in combination with P.A.S., prior to the trial. The other 2 patients are of particular interest, since neither had had any previous chemotherapy and yet both had initially streptomycin-resistant organisms (ratio 8); they are referred to again in the Discussion. These 9 patients are excluded from the following analysis of the development of streptomycin resistance under the SP and SH treatments. The 7 SH patients are referred to again in the section on isoniazid sensitivity, as it was particularly important to investigate whether their bacilli developed resistance to that drug.

There were 3 other patients (2 SP, 1 SH), in whom the streptomycin-sensitivity tests were equivocal. Although the resistance ratio was 4 in two of them, and only 2 in the third, the test organism was inhibited in a concentration of 2 units per ml. in one case, and had grown in 2 units per ml. in the other two (and was not tested further). There was therefore a suggestion that the strains might be resistant. It did not seem correct to class these strains either as initially sensitive or as initially resistant, and these patients too have been excluded from the analysis. The strains from one of the two "doubtful" SP cases remained doubtfully resistant at both one and three months, with sensitivity tests still showing growth in 2 units per ml. (not tested further). Strains from the other patient were resistant (ratio 8) at one month, doubtfully resistant at two and three months, and resistant (ratio 64) at four months. Both these patients gave a previous history of having had streptomycin alone. The SH patient with a doubtfully resistant test initially had no previous history of chemotherapy and gave a definitely sensitive test at two months.

For almost all (95%) of the remaining patients it was established that the organisms were streptomycin-sensitive at the start of treatment. No information was forthcoming for the remaining 5% (7 SP, 4 SH) for technical reasons, such as failure of the primary culture (despite a positive direct test) or of the subculture to grow; for these cases it has been assumed that the organisms were sensitive to streptomycin. Of these 11 patients, 5 on SP and 2 on SH had never had any previous chemotherapy, and a third SH patient had never had streptomycin previously.

* Defined as the ratio of the lowest concentration of streptomycin completely inhibiting growth of the test strain to the corresponding figure for the standard strain (H37Rv).

Results

It is obviously very important to compare the relative effectiveness of the P.A.S. and of the isoniazid in the SP and SH treatments respectively in preventing the emergence of streptomycin resistance. Table IX presents the results of the streptomycin-sensitivity tests after one, two, and three months' treatment with SP or SH (after excluding patients known to be streptomycin-resistant at the start of treatment). The figures in the column headed "culture positive, no sensitivity result available" usually represent failure of a subculture to grow, contamination of the culture, or overheating (incubator fault). For a few of the cases at two and three months in this column, the sensitivity result was still pending at the time of analysis.

TABLE IX.—*Results of Streptomycin Sensitivity Tests in SP and SH Cases, Excluding Those Found to be Streptomycin-resistant on Entry to Trial*

	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests				Total Resistant		
					Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
At 1 month ..	SP	86	37	2	47	46	1	0	1	*2*	*1*
	SH	124	45	4	75	74	1	0	1	*1*	*1*
At 2 months ..	SP	84	49	4	31	30	1	0	1	*3*	*1*
	SH	124	68	4	52	50	1	1	2	*4*	*2*
At 3 months ..	SP	78	53	8	17	13	2	2	4	*24*	*5*
	SH	109	82	8	19	17	2	0	2	*11*	*2*
By disease group at 3 months:											
Group 1	SP	21	14	4	3	3	0	0	0		
	SH	30	23	2	5	5	0	0	0		
Group 2	SP	29	19	4	6	6	0	0	0		
	SH	41	30	3	8	7	1	0	1		
Group 3	SP	28	20	0	8	4	2	2	4		
	SH	38	29	3	6	5	1	0	1		

Table IX shows that at one month a streptomycin-resistant culture was obtained in one out of 47 culture-positive SP cases (2%), compared with one out of 75 culture-positive SH cases (1%). At two months the corresponding figures were one out of 31 culture-positive SP cases (3%), and 2 out of 52 similar SH cases (4%). At three months there were 4 resistant cultures from 17 culture-positive SP cases (24%) (2 of them moderately and 2 strongly resistant); the corresponding figure was 2 from 19 positive SH cases (11%) (both moderately resistant). When the incidence of streptomycin resistance is expressed by a percentage of the total number of patients for whom cultures were *examined* (whether culture-positive or negative—that is, (*c*) expressed as a percentage of (*a*) in Table IX)—the figures at three months are 4 out of 78 SP patients (5%) and 2 out of 109 SH patients (2%). None of these differences is statistically significant.

On the main question—namely, the prevention of streptomycin resistance by the administration of isoniazid with the streptomycin (SH)—the figures in Table IX at three months, though small, are highly suggestive. They indicate that the addition of isoniazid in a dosage of 200 mg. a day is highly effective—indeed, of the same order of effectiveness as 20 g. of sodium P.A.S. a day (or, when less was given, as large a dose of P.A.S. a day as the patient could tolerate).

Streptomycin-sensitivity tests are already available, in addition, at four months for 7 SH patients who had continued on the combination, though at a reduced dosage of streptomycin (1 g. three times a week), during the fourth month. All 7 tests showed that the cultures were sensitive. One of the patients had yielded a resistant strain at a low level (ratio 8) at three months.

5. P.A.S. Sensitivity

The figure of 4 streptomycin-resistant strains from 17 culture-positive SP patients with sensitivity tests at three months does not seem to represent the usual experience of streptomycin resistance after this period of treatment with streptomycin 1 g. daily plus P.A.S. 20 g. daily. In the present series this high figure is in part related to previous chemotherapy with P.A.S. alone. Evidence will be presented in a further report, as well as in a detailed article from one of the co-operating centres, to show that the administration of P.A.S. alone for periods of more than a month is an important factor in the development of streptomycin resistance when a course of streptomycin+P.A.S. is given subsequently. Of the above-mentioned 4 culture-positive SP patients, known to have streptomycin-sensitive strains before treatment but resistant strains at three months, 2 gave a history of prior treatment with P.A.S. alone, and both were P.A.S.-resistant at the start of treatment. By contrast, of the 13 culture-positive patients with streptomycin-sensitive organisms at three months, only one had had P.A.S. alone previously, and this patient's strain was P.A.S.-sensitive at the start of treatment.

6. Isoniazid Sensitivity

The technique was in brief as follows: a loopful of bacterial suspension from a young primary culture on egg medium was spread on each of a series of egg-medium slopes containing graded concentrations of isoniazid of 0, 0.2, 1, 5, 10, and 50 μg. per ml.; a culture of H37Rv was treated similarly in parallel. Both sets of slopes were read at two weeks and at four weeks, and each slope was recorded at each reading in one of five categories: "confluent growth," "innumerable discrete colonies," "100–20 colonies," "less than 20 colonies," "nil." The experience gained since the publication of the first report has served to confirm the satisfactory nature of the criteria of sensitivity recorded in that report, and there appears to be no reason to introduce any modification. A small number of colonies continue to be observed occasionally on isoniazid-containing medium bearing cultures of the test organism, both before and during treatment, as well as of the standard organism, even in concentrations of isoniazid of 10 μg. per ml. This occurrence justifies the earlier decision that such sparse growths should be ignored in assessing the emergence of resistance during treatment. Accordingly, in the analysis of isoniazid resistance, readings of "less than 20 colonies" are classified with "no growth." This end-point has proved very satisfactory from the point of view both of reading the tests and of interpreting the results. A culture is designated "resistant" when growth of 20 or more colonies is observed at four weeks in concentrations of 1.0 μg. isoniazid per ml., or higher, and "of doubtful resistance" in cases of such growth in a concentration of 0.2 μg. per ml., but not more. As before it was found that the development of colonies is often incomplete after two

weeks' incubation, and the results analysed in Table X are derived solely from the four-week reading.

The 7 SH patients known to have streptomycin-resistant organisms at the start of treatment have been excluded from Table X. It was suspected that the behaviour of their organisms in regard to the development of isoniazid resistance under SH treatment might well differ from that of even more impressive; whereas 33 resistant strains were isolated from a total of 93 H patients (35%), only 3 isoniazid-resistant strains were isolated from 109 SH patients (3%) (growth at 1, 5, and 50 μg. per ml. respectively). Again, the benefit to the SH treatment is highly significant.

There is therefore a striking difference between the incidence of isoniazid resistance in patients on isoniazid

TABLE X.—*Results of Isoniazid Sensitivity Tests in H and SH Cases, Excluding Those Found to be Streptomycin-resistant on Entry to Trial*

	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests							Total Resistant		
					Total Results Available (*b*)	Sensitive	Doubtful	Resistant						
						No Growth at 0·2 μg. per ml.	Growth at 0·2 μg. per ml. Not at 1	Growth at 1 μg. per ml. Not at 5	Growth at 5 μg. per ml. Not at 10	Growth at 10 μg. per ml. Not at 50	Growth at 50 μg. per ml.	No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
At 1 month ..	H	102	27	2	73	58	7	3	0	2	3	8	*11*	*8*
	SH	124	45	3	76	67	6	3*	0	0	0	3	*4*	*2*
At 2 months ..	H	105	38	4	63	17	14	7	6†	3	16	32	*52*	*30*
	SH	124	68	2	54	46*	3	5	0	0	0	5	*9*	*4*
At 3 months ..	H	93	36	4	53	11	9	6	6†	6	15	33	*62*	*35*
	SH	109	82	4	23	18	2	1	1	0	1	3	*13*	*3*
By disease group at 3 months:														
Group 1	H	21	11	0	10	3	1	0	0	3	3	6		
	SH	30	23	1	6	6	0	0	0	0	0	0		
Group 2	H	33	15	4	14	3	3	2	1	0	5	8		
	SH	41	30	2	9	7	1	0	0	0	1	1		
Group 3	H	39	10	0	29	5	5	4	5†	3	7	19		
	SH	38	29	1	8	5	1	1	1	0	0	2		

* One result was obtained from a guinea-pig culture.
† One of these cultures showed growth at 5 μg. per ml., but was not tested at higher concentrations.

patients with initially streptomycin-sensitive organisms; it is shown below that this was so. In order that Table X should present data for comparable groups, 5 H patients whose bacilli were subsequently found to be streptomycin-resistant before treatment were also excluded, although for these patients there was no *a priori* expectation that resistance to streptomycin would influence the development of resistance to isoniazid under that drug alone. These 5 H cases are also considered separately below.

Results

Table X sets out the results of the isoniazid-sensitivity tests at one, two, and three months in H and SH cases (after excluding patients known to be streptomycin-resistant at the start of treatment). Of 80 isoniazid-sensitivity tests on positive cultures from H patients before treatment, there had been 5 "doubtful" and no "resistant" strains. Examination of 100 SH patients' cultures before treatment also yielded 5 "doubtful" and no "resistant" strains.

At one month, from 73 culture-positive H patients with sensitivity results, 8 resistant cultures (11%) (5 at a level of 10 μg. per ml. or higher) and 7 doubtfully resistant cultures (10%) were obtained; 76 similar SH patients yielded 3 instances of isoniazid resistance (4%, all resistant at the lowest level) and 6 of doubtful resistance (8%). The differences are suggestive, but not statistically significant.

At two months, resistant cultures were obtained from 32 (52%) of 63 culture-positive H patients (half of these growing at 50 μg. per ml.), and another 14 patients (22%) yielded doubtfully resistant strains. The corresponding SH results from 54 culture-positive patients were 5 resistant cultures (9%) and 3 doubtful (6%); again resistance was at a low level (growth at 1 μg. per ml. but not 5). The benefit to the SH treatment is highly significant statistically.

At three months, the proportion of resistant strains from patients on isoniazid alone had increased to 33 (62%) from 53 culture-positive patients, compared with only 3 (13%) of 23 positive SH cultures. When the incidence of isoniazid resistance is expressed as a percentage of the total number of patients for whom cultures were *examined* (whether culture-positive or negative—that is, (*c*) expressed as a percentage of (*a*) in Table X), the difference at three months is alone and in those having the combination isoniazid + streptomycin. The combination largely prevents the development of isoniazid resistance.

Turning now to the 7 SH patients in whom streptomycin-resistant strains were isolated before treatment, 4 had produced isoniazid-resistant strains at the end of three months. The other 3 were culture-negative at three months, but one was known to have had sensitive strains at two months, and another at both two months and four months. Although the numbers are very small, they suggest that this group of patients is behaving more like a group treated with isoniazid alone than a group treated with the combination streptomycin + isoniazid. In other words, patients with streptomycin-resistant organisms are not protected from the development of isoniazid resistance by the SH treatment.

Of the 5 H patients with streptomycin-resistant organisms initially, the bacilli of 1 were also isoniazid-resistant before treatment. In this case the organisms grew at 1 but not 5 μg. per ml. in the pre-treatment test. The organisms showed the same degree of resistance at one, two, and five months, but at four months growth occurred in the 5 μg. per ml. tube; the culture was negative at three months. This strain was non-pathogenic to guinea-pigs and mice, and therefore appears to be non-virulent (this case will be reported later). Of the strains from the other 4 patients, one was resistant at three months and one sensitive. The other two patients were culture-negative at three months, but had resistant organisms at four months (the culture from one had been doubtfully resistant at one month). The behaviour of these four cases is in keeping with the behaviour of the rest of the H cases.

Isoniazid-sensitivity tests are also available at four months for 8 patients who had continued on streptomycin + isoniazid, in full dosage in one, but with a reduced streptomycin dosage of 1 g. three times a week in 7. Of these 8 patients, 4 had isoniazid-sensitive organisms (including the patient on daily streptomycin), one was doubtful, and 3 were definitely resistant (growth in 5, 10, and 50 μg. per ml. respectively). The strain from one of the 3 resistant cases was known to have been resistant at two months. There were no sensitivity tests available on the

other 2 between one month, when sensitive organisms were found, and the resistant results at four months, and they may well have developed resistance before the fourth month. Clearly this experience beyond three months' treatment with streptomycin + isoniazid indicates the need for a most careful evaluation in the light of further results when they become available.

When the data are complete it will be important to determine whether, when the bacilli of patients on streptomycin + isoniazid become resistant to one of the drugs, they become resistant to the other as well. The results of streptomycin- and isoniazid-sensitivity tests at three months in SH cases given in Tables IX and X have been derived from 23 patients. Results of isoniazid-sensitivity tests were available for all 23, whereas the results of streptomycin-sensitivity tests were available for only 19. No conclusions can be drawn from this limited information, but the findings were as follows :

		Streptomycin Sensitivity at 3 Months		
		Resistant	Sensitive	Test Pending
Isoniazid sensitivity at 3 months	Resistant	1	1	1
	Doubtful	1	0	1
	Sensitive	0	16	2

IV. DISCUSSION

In the design of the present trial there were two main departures from the plan of the earlier Medical Research Council trials of chemotherapy in pulmonary tuberculosis. One was the decision to increase the range and scale by including several different types of case, and by enlisting the co-operation of a large number of hospitals. The other arose from the realization that a rapid intake of cases would make it imperative to review the results continually if clinical material was not to be wasted, and if the best forms of treatment were to be introduced without undue delay. A system of monthly progress reports for each patient was therefore set up, and the continual analysis permitted the early publication of a report in which the effects of streptomycin + P.A.S. were compared with those of isoniazid alone (Medical Research Council, 1952).

Even before the publication of this first report it had become apparent that the effects of the combination streptomycin + isoniazid should also be studied, and this treatment was introduced from June 1, 1952, in all three disease groups of the trial, concurrently with the treatments already mentioned. As further knowledge about the effectiveness and limitations of the new drug accumulated, the trial was modified again in order to study exclusively the value of combining isoniazid with other anti-tuberculosis drugs. The trial therefore differs from earlier clinical trials because it has developed on a flexible pattern and has been modified to study fresh problems in the light of information it has itself yielded. This flexibility is one of the most valuable characteristics of the present trial, since it enables much more information to be gained from the available clinical material.

The present observations relate to 364 patients suffering from pulmonary tuberculosis and treated for three months—142 with streptomycin + isoniazid, 102 with streptomycin + P.A.S., and 120 with isoniazid alone. These three treatments were allocated concurrently and at random. The results at the end of three months are summarized in Table XI and also in Figs. 2 to 8. The analysis shows that over this limited period streptomycin + isoniazid is superior to streptomycin + P.A.S. in lowering the sedimentation rate and in increasing body weight, and rather better in improving the general condition. The two treatments have a similar effect upon pyrexia, upon the presence of tubercle bacilli in the sputum, and, most important, upon radiographic appearances. Streptomycin + isoniazid, compared with isoniazid alone over a three-month period, is found to be considerably more effective in lowering the sedimentation rate, in suppressing tubercle bacilli in the sputum (confirming the findings of Dye, Lynch, and Brees, 1953), and also in improving the radiographic appearances. It is slightly more effective in resolving pyrexia. The two treatments produce equally striking improvements in general clinical condition and in weight.

TABLE XI.—*Summary of Comparisons of Streptomycin Plus Isoniazid with Streptomycin Plus P.A.S., and with Isoniazid Alone, at the End of Three Months' Treatment*

	Streptomycin Plus Isoniazid %	Streptomycin Plus P.A.S. %	Isoniazid %
General condition:			
Improvement 2-plus	35	24	27
,, 1-plus	51	51	52
No change	13	22	18
Deterioration	0	2	3
Death	1	2	1
Weight:			
Gain 14 lb. (6·35 kg.) or more	42	13	47
,, 7–13 lb. (3·2–5·9 kg.)	40	32	29
,, less than 7 lb., or no change	15	39	20
Loss	3	15	4
Temperature:			
Afebrile at 3 months (febrile at start)	82	76	68
Sedimentation rate:			
Fall to normal from 21 or more in 3 months	45	21	25
Radiograph:			
Improvement 2-plus or 3-plus	38	31	22
,, 1-plus	26	32	32
No change	33	33	36
Deterioration	2	1	9
Sputum:			
At 3 months: Direct positive	18	29	41
Positive culture only	15	16	23
Negative	67	55	37
Isoniazid sensitivity:			
At 3 months: Sensitive	78	—	21
Doubtful	9	—	17
Resistant.	13	—	62

See the text for the streptomycin-sensitivity results, and Figs. 2–8 for the numbers of patients on which these percentages are based.

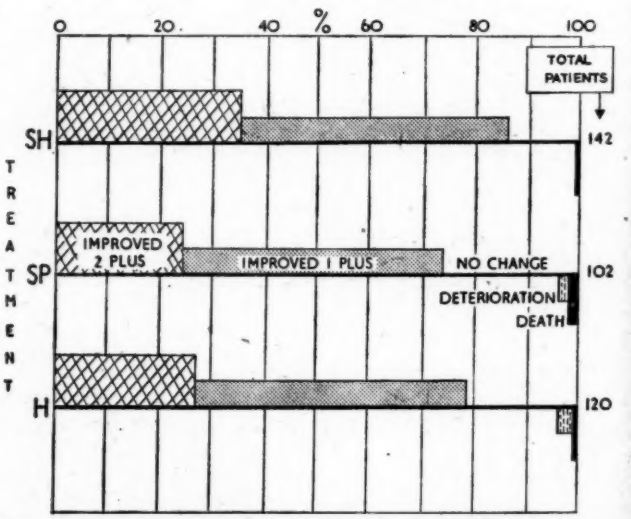

FIG. 2.—Changes in general condition in the first three months in the three treatment series. Each category of response is expressed as a percentage of the total patients.

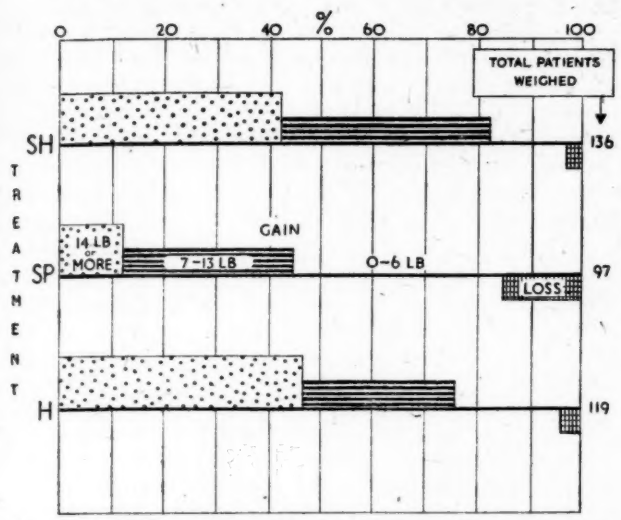

FIG. 3.—Weight changes in the first three months in the three treatment series. Each category of response is expressed as a percentage of the total patients weighed.

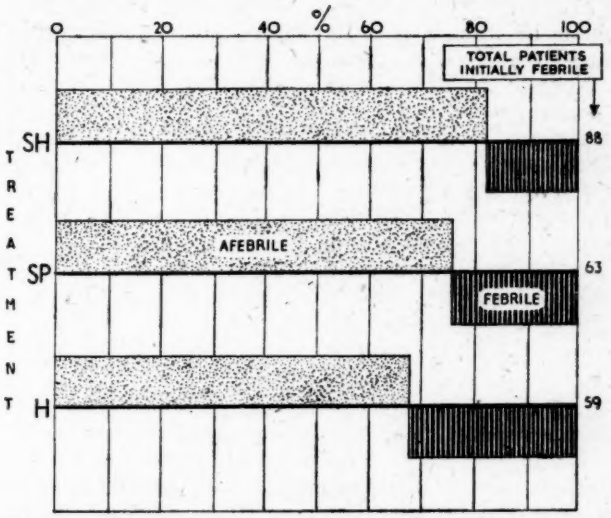

FIG. 4.—Temperature at three months in patients febrile during pre-treatment week. The response is expressed as a percentage of the total patients initially febrile.

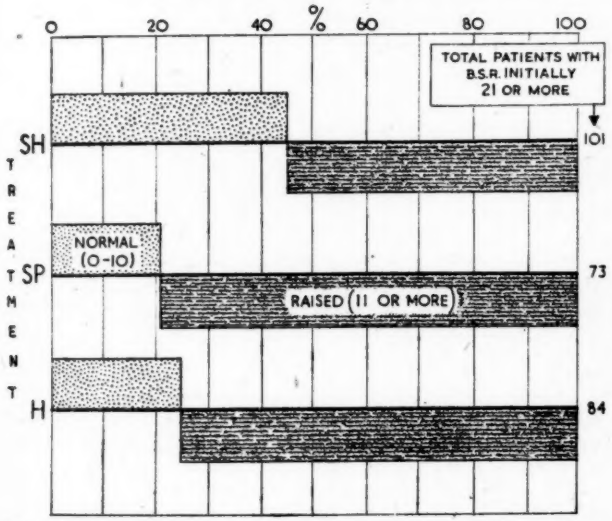

FIG. 5.—Sedimentation rate at three months in patients with a sedimentation rate of 21 or more pre-treatment. The response is expressed as a percentage of the total patients with initially raised B.S.R.

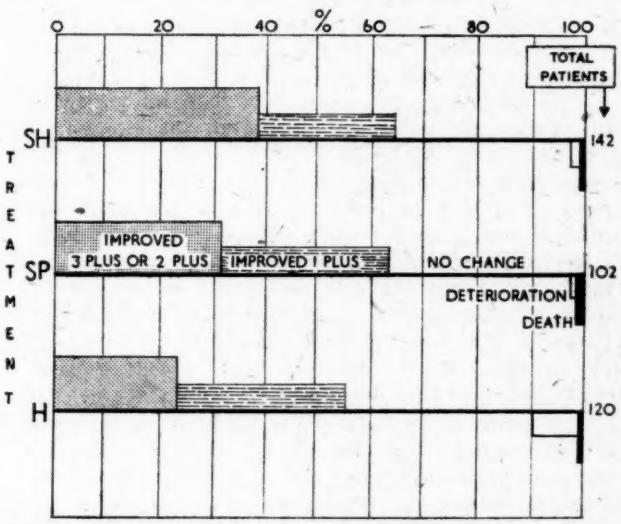

FIG. 6.—Changes in radiographic appearances in the first three months. Each category of response is expressed as a percentage of the total patients.

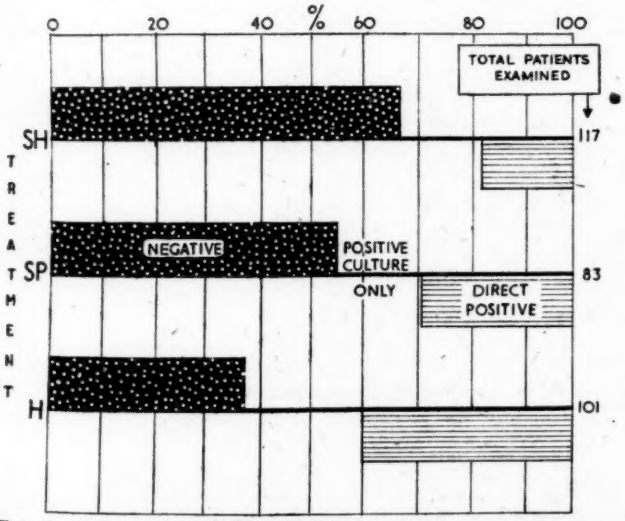

FIG. 7.—Presence of tubercle bacilli at a single examination at three months. The results are expressed as percentages of the total patients examined.

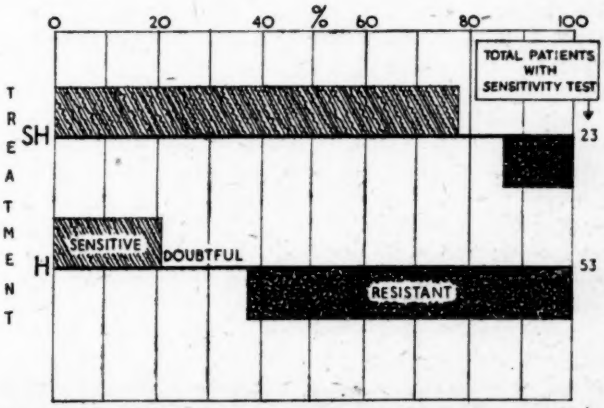

FIG. 8.—Isoniazid sensitivity in SH and H patients at three months. The results are expressed as percentages of the total patients with sensitivity tests

Although there has been virtually no toxicity from isoniazid with the dosage used, its combination with streptomycin suffers from the disadvantage of toxic reactions to the streptomycin. In the present series such reactions were severe enough to lead to withdrawal of the patient from the trial in 4% of cases (6 out of 148). On the other hand, streptomycin + isoniazid produces far fewer side-effects than streptomycin with P.A.S. in a dosage of 20 g. daily, and is also less unpleasant for the patient. Summarizing, it may be concluded that over a three-month period streptomycin 1 g. daily + isoniazid 200 mg. daily is clinically the most effective anti-tuberculosis chemotherapy yet investigated in this trial, although its superiority to streptomycin 1 g. daily + P.A.S. 20 g. daily is not great.

An important defect of the use of isoniazid by itself is the frequent and rapid emergence of bacterial resistance to the drug. In the present series of patients treated with isoniazid alone, 11% of cultures positive at one month were resistant, 52% of those at two months, and 62% of those at three months. The corresponding figures for the patients treated with streptomycin + isoniazid were only 4% isoniazid-resistant cultures at one month, 9% at two months, and 13% at three months. Moreover, when, with the combined drugs, isoniazid resistance did develop, the average level of this resistance was much lower than for patients on isoniazid alone. The administration of streptomycin 1 g. daily with isoniazid 200 mg. daily therefore lessens considerably the proportion of cases in which isoniazid-resistant strains, particularly those of high resistance, emerge over a three-month period. The very limited information on isoniazid resistance available at four months for these patients is, however, a little disquieting. If, with larger numbers, a substantial incidence of resistant strains appears, it will be important to assess what part, if any, is played by reducing the dosage of streptomycin in the fourth month.

It must be remembered that an increasing proportion of bacteriological specimens from patients on each of the three treatments studied here was found to be negative on culture as treatment proceeded, and consequently fewer and fewer sensitivity tests could be performed. Because of this, it can be argued that the figures quoted above, expressing the resistant strains as a percentage of the positive cultures on which sensitivity tests were performed, do not give an entirely fair picture of the development of resistance; they omit the culture-negative patients, some of whom will be permanently negative. An alternative presentation of the findings is that at three months 33 resistant cultures were obtained from a total of 93 of the patients on isoniazid alone (35%), compared with only 3 from a total of 109 of the patients on streptomycin + isoniazid (3%). On the other hand, these percentages give an unduly favourable impression of the incidence of resistance at three months, partly because not all the culture-negative patients will be permanently negative, and partly because a few sensitivity tests are still pending at three months. A true measure of the incidence of isoniazid resistance at three months in patients not permanently negative probably lies somewhere between 62% and 35% for those on isoniazid alone, and between 13% and 3% for those on streptomycin + isoniazid.

Of 7 patients on streptomycin + isoniazid whose organisms were initially streptomycin-resistant, 4 yielded cultures resistant to isoniazid at three months. The behaviour of this small group of patients is more akin to that of patients on isoniazid alone than to that of patients on streptomycin + isoniazid. In other words, if a patient's organisms are streptomycin-resistant initially, the combination streptomycin + isoniazid apparently affords no protection against the risk of the development of isoniazid resistance.

For the patients treated with streptomycin + isoniazid it is also important to know whether the combined therapy prevents the emergence of bacilli resistant to streptomycin. The analysis has shown that this is so. At three months, two streptomycin-resistant strains were isolated from 19 positive cultures (11%); these two strains were obtained from a total of 109 patients (2%). The true incidence of streptomycin resistance at three months in patients not permanently negative probably lies between these two percentages. The corresponding figures for isoniazid resistance in the same patients were 13% and 3%. Thus, the combination streptomycin + isoniazid appears to be as effective for three months in preventing the development of streptomycin-resistance as of isoniazid resistance. The very limited information on streptomycin sensitivity available at four months for patients on the combination is satisfactory. However, it will be appreciated that, if isoniazid resistance should prove to be a problem at four months, there is a risk that streptomycin resistance may also emerge after a delay of one or two further months if treatment with streptomycin + isoniazid is continued.

For a period of three months streptomycin + P.A.S. and streptomycin + isoniazid are of the same order of effectiveness in preventing the development of streptomycin resistance. However, evidence, which will be presented later, has emerged in the course of the trial that the administration of P.A.S. alone carries with it a serious risk that P.A.S. resistance will develop; if it does, and the patient is subsequently treated with streptomycin + P.A.S., the combination no longer provides protection against the development of bacillary resistance to streptomycin. These findings are particularly important because the use of P.A.S. alone is still regarded by many clinicians as an acceptable treatment for pulmonary tuberculosis. The conclusion of the Therapeutic Trials Committee of the Swedish National Association against Tuberculosis (1952), that P.A.S. alone "should be given in cases where a moderate effect is wanted for a rather long time," seems unwarranted in view of these bacteriological findings.

The lessons to be learnt from these apparently complicated findings concerning the development of bacterial resistance are simple, and are as follows:

(1) *None of the three drugs, isoniazid, streptomycin, or P.A.S., should be used by itself in the treatment of pulmonary tuberculosis.* Equally, no new drug should at first be used by itself, except in clinical trials carefully planned to ascertain its bacteriological qualities as well as its clinical efficacy.

(2) To give a combination of two of these drugs to a patient whose organisms are already resistant to one of the two appears to be tantamount to giving the other alone, and so is equally undesirable. *It is therefore essential, whenever possible, to test the drug sensitivity of a patient's organisms before a course of chemotherapy is started, so that any unsuitable combination of drugs may be avoided and a potentially effective combination for that patient used instead.*

(3) The procedures for the assessment of drug resistance are at present slow and not always satisfactory, and many clinicians, when confronted with an ill patient, will not wish to risk further deterioration before instituting some form of chemotherapy. *A careful scrutiny of the history of previous chemotherapy, with particular regard to any drug which has been given alone, may warn the clinician of possibly unsuitable combinations, but such information cannot be regarded as a substitute for sensitivity tests, which should always be undertaken as soon as possible.*

(4) Even in newly diagnosed cases it is no longer safe to assume that the tubercle bacilli are fully sensitive; since the start of the present trial 4 out of 279 previously untreated patients whose bacilli were tested for initial streptomycin sensitivity (1%) have been found to have organisms resistant to streptomycin; there is evidence that these cases may have been infected with resistant strains. (A full report will appear later.) With the increasing use of anti-tuberculosis drugs the present low risk of becoming infected with drug-resistant bacilli may well increase. *If, therefore, chemotherapy must be initiated for a newly diagnosed case in the absence of sensitivity results, the clinician should inquire into previous chemotherapy and the results of sensitivity tests in any known contact before deciding upon a treatment combination.*

(5) There is, in fact, a great need for simple, reliable, and speedy techniques both for the culture of tubercle bacilli and for the determination of their sensitivity to chemotherapeutic agents. In the meantime *it is recommended that every patient with pulmonary tuberculosis, if still bacteriologically positive on completing a course of chemotherapy, should have further sensitivity tests performed as a routine.* This information would then be available if more chemotherapy is required at a later date, or should one of the patient's contacts develop the disease. However, the possibility that a drug-resistant strain may be replaced by a sensitive variant after the cessation of treatment must be kept in mind.

Finally, the Committee has obtained convincing evidence that streptomycin 1 g. daily + isoniazid 100 mg. twice a day is a highly effective combination of drugs when used for a period of three months in the treatment of pulmonary tuberculosis. On none of the clinical or bacteriological criteria was the combination inferior to streptomycin 1 g. daily + P.A.S. 5 g. four times a day over this period; in two respects—namely, in lowering the sedimentation rate and in fostering weight gain—it was decidedly superior. Nevertheless, the slender evidence on bacterial resistance which is available after four months' treatment is not entirely reassuring. In view of the short period of observation it is certainly not yet possible to assess the final place of streptomycin + isoniazid in the chemotherapy of pulmonary tuberculosis. The evaluation will depend to a considerable extent upon the clinical and bacteriological findings in patients treated with this combination of drugs over a longer period of time, in comparison with streptomycin + P.A.S. and other forms of chemotherapy.

The trial is continuing, and at present two different dosages of streptomycin and two of P.A.S. are being used, each in combination with isoniazid. These investigations are indispensable in determining the most effective ways in which isoniazid should be used in the treatment of pulmonary tuberculosis.

V. SUMMARY

As part of a clinical trial of isoniazid (isonicotinic acid hydrazide) in the treatment of pulmonary tuberculosis, 364 patients from 40 hospitals were studied; 142 were treated with streptomycin (1 g. daily) + isoniazid (100 mg. twice a day), 102 with streptomycin (1 g. daily) + P.A.S. (sodium salt, 5 g. four times a day), and 120 with isoniazid (100 mg. twice a day) alone. When submitting a case the physician did not know which treatment the patient would receive, this being determined by random allocation. The present report analyses the results at the end of three months' treatment and observation.

Three main groups were observed: Group 1, acute rapidly progressive disease of recent origin (excluding, from this report, bilateral disease between the ages of 15 and 30); Group 2, other forms suitable for chemotherapy; Group 3, chronic disease considered unlikely to respond to chemotherapy.

On admission, the three treatment series had a similar distribution of patients with severe and less severe illness.

At the end of three months, the general condition of the majority of patients had improved, but in this respect the differences between the three treatment series were small. The average gains in weight during the period were 13 lb. (5.9 kg.) for those on streptomycin + isoniazid (SH), 6 lb. (2.7 kg.) for those on streptomycin + P.A.S. (SP), and 13 lb. for those on isoniazid (H) alone.

The temperature of febrile patients fell to normal in 82% of SH, 76% of SP, and 68% of H cases. In patients with a sedimentation rate of 21 or more before treatment, the rate fell to 10 or less in 45% of those on SH, compared with only 21% on SP and 25% on H.

Changes in radiographic appearances were independently assessed by a radiologist unaware of the treatment of any patient. Two-plus or 3-plus improvement was seen in 38% of SH, 31% of SP, and 23% of H cases. There was little difference, over the whole range of response, between patients on SH and SP, but the patients on these treatments responded better than those on H. There were three radiographic deteriorations and one death on SH, one deterioration and two deaths on SP, and 11 deteriorations and one death on H.

The proportions of patients bacteriologically negative, both on direct examination and on culture, at a single examination at three months, were 67% for the SH series, 55% for SP, and 37% for H.

It is concluded, *judging solely from the results at three months,* that streptomycin + isoniazid, with the dosages used, is clinically the most effective of the treatments studied, although its superiority to streptomycin 1 g. daily + P.A.S. 20 g. daily is not great. A full evaluation must await a longer period of observation.

Bacillary resistance to isoniazid was found in 62% of culture-positive H patients tested at three months, compared with only 13% for similar SH patients. Bacillary resistance to streptomycin was found in 11% of these SH patients at three months. Thus the combination streptomycin + isoniazid, with the dosages studied, is as effective for three months in preventing the development of streptomycin resistance as of isoniazid resistance. Further, for three months the SH treatment is as effective as the SP treatment in preventing the emergence of bacilli resistant to streptomycin.

Patients with organisms initially streptomycin-resistant were apparently not protected from the risk of development of isoniazid resistance by the SH treatment;

patients with organisms initially P.A.S.-resistant (who had had prior treatment with P.A.S. alone) were not protected from the risk of development of streptomycin resistance by the SP treatment. Thus none of the three drugs, isoniazid, streptomycin, or P.A.S., should be used by itself, nor should two of them be used in combination for a patient whose organisms are already resistant to one of the pair. Whenever possible, the drug sensitivity of a patient's organisms should be assessed before chemotherapy is started, to avoid an unsuitable combination of drugs; and also on its completion, in case more chemotherapy is required later.

There is a great need for simple, reliable, and speedy techniques for the culture of tubercle bacilli and for the determination of their sensitivity to chemotherapeutic agents.

The trial was designed so that it could be modified to study fresh problems in the light of information it had itself yielded; at present the effects of two different dosages of streptomycin and two of P.A.S., each in combination with isoniazid, are under investigation.

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The above cannot be a comprehensive list of all the doctors who have contributed to the results reported here, nor has it been possible to name the many laboratory technicians who have done detailed and valuable work. The Tuberculosis Chemotherapy Trials Committee expresses its thanks to all members of hospital staffs who have assisted in the investigation, particularly for their willing response to the urgent requests for information for inclusion in this report.

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REFERENCES

Dye, W. E., Lynch, H. P., and Brees, A. G. (1953). *Amer. Rev. Tuberc.*, **67**, 106.

Medical Research Council (1948). *Lancet*, **2**, 862.

—— (1952). *British Medical Journal*, **2**, 735.

Swedish National Association against Tuberculosis (1952). *Acta tuberc. scand.*, **27**, 157.

M. CANIS RINGWORM AND LOSS OF SCHOOLING

BY

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Cases of ringworm of the scalp produced by the two commonest pathogens, *Microsporum canis* and *M. audouini*, continue to be grouped together as one condition from the point of view of treatment. This is unfortunate. *M. canis* ringworm differs from the *M. audouini* type in being amenable to simpler measures of treatment and in being less contagious. Further, it can be demonstrated that there is no valid reason for excluding *M. canis* cases from school. In the treatment of *M. audouini* ringworm, *x*-ray epilation is unquestionably the correct procedure, and if it is not carried out the child may continue with the complaint until puberty is reached. As the technique of epilation improves, so do the risks inherent in its use diminish.

In common with others treating ringworm of the scalp, I have experienced the following difficulties. There has been an occasional case of incomplete regrowth of hair; cases in which a marked inflammatory reaction resulted, necessitating incision of sterile abscesses (Fig. 1); and cases in which the first epilation failed to eradicate the infection. Occasionally an anaesthetic has been necessary in toddlers. After *x*-ray epilation a good regrowth of hair has taken six months in boys and up to a year in girls.

Scalp ringworm caused by *M. canis* need never be treated by *x*-ray therapy, the following measures of treatment being effective in all cases. The scalp is clipped and the hair kept short, a linen cap is worn constantly, and a simple fungicidal ointment is applied daily. The mildest fungicides are effective, and Whitfield's ointment is adequate. Far stronger fungicides and rubefacients are tried from time to time in cases of *M. audouini* ringworm, but, as yet, no completely effective application has been found. There is no justification for their use in *M. canis* ringworm.

Sharp (1951) described his treatment of 120 cases of *M. canis* ringworm of the scalp (*M. audouini* ringworm is extremely rare in Australia). He used fungicidal treatment only, and the average time taken for cure was 13 weeks. In the subsequent discussion it was apparent that many dermatologists still use *x*-ray epilation in *M. canis* cases simply because by this method it is possible to get the child back to school in about six weeks.

Distinction Between Types

M. canis and *M. audouini* ringworm cases may be distinguished with reasonable accuracy clinically but only with certainty on culture. It is essential to know which type is endemic locally. For many years a focus of *M. audouini* scalp ringworm has existed in the Blackwood area of Monmouthshire, but practically none of this type of ringworm has been encountered in Newport, 12 miles distant. Of the ringworm cases in the Blackwood area, 91 out of 94 cases have been of *M. audouini*, and in the Newport area out of 32 cases only one has been produced by *M. audouini*.

There are other factors which enable one to make a clinical diagnosis of *M. canis* ringworm. Local tissue reactions are usually more pronounced and there may be erythema, papulation, or even kerion. This distinction, however, is not entirely reliable, and, exceptionally, *M. audouini* cases produce inflammatory reactions (Fig. 2). There is usually a history of an infected puppy or kitten

with which the patient has come in contact. The frequency of tinea circinata in *M. canis* ringworm is well known (Fig. 3). Beare and Cheeseman (1951), describing 1,004 cases occurring in Northern Ireland between May, 1949, and July, 1950, refer to greater brilliance and longer duration of Wood's light fluorescence in *M. audouini* infections. By applying these tests they were able to diagnose correctly 97% of their 71 *M. canis* infections before the results of culture were available.

Epidemiology

While there is abundant evidence that *M. canis* infections are caught direct from animals, it is rarely possible to demonstrate direct contagion from child to child. In the 27 cases dealt with in Table I, six animals were known to be responsible for 11 cases. Five of the animals were kittens, which were destroyed.

In other cases some association with a domestic animal was invariable, but this alone is not proof of an animal source of contagion. The possibility of one animal being responsible for multiple cases must not be lost sight of, and the four children with the non-pigmented subtype (Cases 20–23) were all infected by one dog. Roberts (1909) described the direct infection of 13 persons from a single cat. Thomas, Lennox, and Duncan (1945) reported the infection of nine persons from one dog. Kittens are now recognized as the more usual sources of *M. canis* infections.

TABLE I.—*Analysis of M. canis Scalp Ringworm Cases*

Case No.	Age (yrs)	Date First Seen	Date Discharged	Prior Absence from School	School*	M. Canis Type	Contacts
1	12	24/10/50	19/12/50	3 days	A Mixed	Orange	Siblings
2	9	24/10/50	12/3/51	2 ,,	B Girls	,,	
3	3	24/10/50	19/12/50	—	—	,,	
4	5	27/11/50	19/3/51	3 weeks	A Infants	Citreous	Cousins infected by kitten
5	7½	27/11/50	23/4/51	1 week	A ,,	,,	
6	10	12/12/50	2/4/51		1 Mixed	,,	
7	6	15/12/50	2/4/51		1 ,,	,,	
8	6	19/12/50	11/6/51	6 weeks	C Infants	,,	
9	5	22/1/51	16/4/51	7 ,,	D Boys	,,	Siblings infected by kitten
10	8	22/1/51	16/4/51	9 ,,	D ,,	,,	
11	7	23/1/51	23/4/51	20 ,,	E Junior	,,	
12	7	31/1/51	10/4/51	6 ,,	F Boys	Orange	
13	9	26/2/51	23/4/51	6 ,,	G ,,	Citreous	Infected by kitten
14	6	12/3/51	11/6/51	6 ,,	D Infants	Orange	,, ,,
15	7	4/6/51	30/7/51	3 ,,	2 ,,	,,	
16	4	27/8/51	13/1/52	Nil	H ,,	Citreous	
17	6	17/8/51	Left district	8 weeks	I Mixed	,,	
18	7	27/8/51	22/10/51	12 ,,	J ,,	,,	
19	8	24/9/51	5/11/51	6 ,,	2 ,,	Orange	
20	9	22/10/51	8/2/52	4 days	K ,,	Non-pigmented	Siblings infected by dog
21	4	22/10/51	8/2/52	—	—	,,	
22	7	22/10/51	8/2/52	1 week	K Mixed	,,	
23	11	12/11/51	17/3/52	2 weeks	L Infants	,,	Infected by same dog
24	6	2/12/51	18/12/51	8 ,,	I ,,	Orange	
25	9	4/2/52		2 ,,	2 ,,	,,	
26	11	8/2/52	3/3/52	Nil	3 Mixed	,,	
27	9/12	3/3/52		—	—	Non-pigmented	

*Lettered schools=Newport County Borough; numbered schools=Monmouth County.

Walker (1950) has studied closely the geographical distribution of the dermatophytes. She reported that *M. canis* tended to form local pockets of infections in certain areas, and notably at Leicester, Leeds, Coventry, Reading, Portsmouth, Barnstaple, and villages in South Devon. She thought there was reason to believe that a high percentage of cases were due to child-to-child contacts, but agreed that complete data on transmission were not usually available. She indicated also the tendency for *M. canis* infection to be attenuated by child-to-child transmission, a renewal of the infection from an animal host being therefore necessary for the continued propagation of the disease on children. Referring to the predominance of one organism in certain areas, Dr. Walker thought that the apparent absence of overlapping of the different infections in the small endemic areas suggested that the predominance of one type tended to prevent establishment of another type in the area.

For purposes of contact tracing it is convenient that *M. canis* can be subdivided into three distinct types, distinguishable on culture by the kind of pigmentation they produce in the medium. The first is the orange type, originally labelled *M. felineum*; the second is the pale yellow or citreous type described by Duncan (1948); and the third is the non-pigmented type, formerly known as *M. lanosum*.

Loss of Schooling

In *M. audouini* cases *x*-ray epilation, if it can be arranged immediately, ideally may enable the child to return to school in about six weeks. The objection to the conservative treatment of *M. canis* cases has been that longer periods of absence from school have been required and an average period of surveillance of about 13 weeks was necessary in Sharp's cases. In the present series the average period of surveillance was exactly 13 weeks.

Beare (1952, private communication) did not find quite the same disparity in the periods of absence required. He concluded that the average time away from school for *M. audouini* cases, assuming that all are epilated and allowing the child to go back to school when he is negative to Wood's light but before much regrowth of hair has taken place, is only slightly less than for *M. canis* cases which are allowed to clear without epilation.

In Newcastle-upon-Tyne, Dixon (1948) reported the occurrence of 1,258 cases over a period of six years. All were excluded from school, although this measure was applied

FIG. 1.—Unusual scalp reaction following *x*-ray epilation in a case of *M. audouini* ringworm.

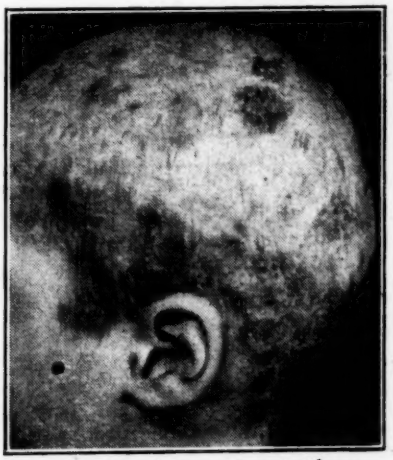

FIG. 2.—Case of *M. audouini* ringworm with exceptional degree of reaction, shown as crusting and papulation.

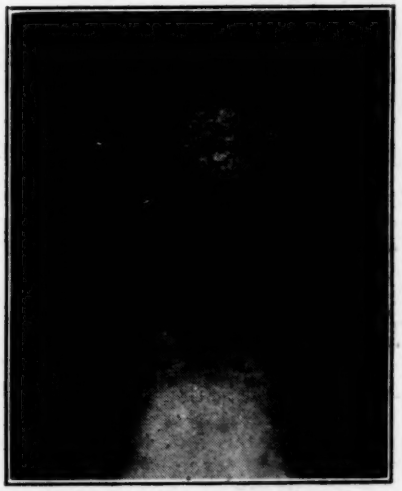

FIG. 3.—Typical *M. canis* infection of scalp with multiple small lesions on glabrous skin of neck.

with some reluctance because the disease is of such a long-term nature as to result in the loss of a high percentage of a child's school career. The cases were of the *M. audouini* type, and the average period of absence from school was assessed as 180 days if the treatment was by ointment and manual epilation. If *x* rays were used an effort was made to have the children back in school in three weeks after irradiation.

Carslaw (1951) treated 208 cases of tinea tonsurans, all mainly *M. audouini* type, and found that the 104 children of school age were able to return to school in an average of 45 days.

It is usual to discuss the period of treatment and surveillance but to overlook the period of absence from school before special treatment is sought. In the children dealt with in Table I this period varied between 1 day and 20 weeks. A variety of excuses, mostly unsatisfactory, were offered, but the fact remained that some children, with either type of microsporosis, managed to evade both school and clinic, while at the same time mixing with siblings at home and playmates in the street. The mean loss of schooling before attending clinic in these cases was 33 days. This figure must be added to the 91 days of surveillance when estimating the average loss of schooling which would have been entailed by the attack of scalp ringworm had the children been excluded. It would thus have amounted to 124 days. (Holiday periods have not been deducted from these figures.)

National Survey

In order to assess the incidence of scalp ringworm in England and Wales a questionary was circularized to 104 major education authorities. The results are summarized in Table II. The following facts emerged.

(*a*) *Prevalence.*—There was a rise in incidence towards the end of the last war and in the immediate post-war years, but this seems to be subsiding again. That scalp ringworm is a problem only of the minority of regions is shown by the fact that in 63 areas the number of cases occurring annually is now either very low or nil. In Table II the figures quoted refer to the last year for which full information was available, and is usually 1951, although 1950 is taken in a few instances. As examples, Bristol had 131 cases, Liverpool 82, Newcastle-upon-Tyne 136, Northumberland 65, Reading 48, Durham 58, and Monmouthshire 42 in 1951.

TABLE II.—*Summary of Replies to Questionary Received from 91 Major Education Authorities. Both M. canis and M. audouini Types of Scalp Ringworm are Included*

		Exclusion from School		Recent Annual Case Incidence			
		Total	Conditional	0–10	11–20	21–30	31+
County councils	29	23	6	16	5	3	5
County boroughs	62	58	4	47	6	4	5
Total ..	91	81 (89%)	10 (11%)	63	11	7	10

(*b*) *Routine Culture.*—Some 42 authorities (46.1%) stated that cultures from infected hairs were taken as a routine. Particulars were not usually available, however, because the patients were dealt with in the dermatological departments of hospitals. Where information was obtainable it was shown that in the county boroughs *M. canis* was predominant in 12, *M. audouini* in 7, and the infections were mixed in 4. In county areas *M. canis* was preponderant only in 2, whereas *M. audouini* was found in 10, 3 areas showing a mixture.

(*c*) *Exclusion from School.*—This is rigidly enforced for all types of scalp ringworm by 89% of authorities. Four county boroughs and five county councils allow some relaxation of this rule, but in none of these areas is ringworm common. The usual condition insisted upon is that the lesions are capable of being adequately covered by some form of headwear. In one district single cases are excluded, but if several children are infected simultaneously they are allowed to attend school with head coverings. Exclusion was enforced in all the localities where *M. canis* is the endemic infection.

Present Investigation

The number of *M. canis* cases in Newport was only 14 between 1945 and 1950, but at the end of the latter year the incidence rose sharply. It was decided to allow all children with *M. canis* ringworm to return to school immediately, provided that certain precautions were observed. The precautions consisted in the wearing of a linen covering or a cap, the use of the ointment provided, and the weekly attendance at the ringworm clinic. The school health authorities willingly co-operated in this plan. Few objections were raised from any quarter. Parents were gratified that their children were able to continue at school, and satisfaction was felt at the clinic because regular weekly attendance was ensured, A solitary complaint was expressed from one child, who felt self-conscious about his headgear.

Details of the plan were as follows. At the first visit of the child to the ringworm clinic a decision was made regarding the probable nature of the dermatophyte and a specimen for culture was taken. A printed list of instructions was then handed to the parent with a promise that if clipping was adequately carried out and the other instructions were followed the child would be allowed to return to school. At his next visit to the clinic a certificate was issued stating that the child was suffering from a type of ringworm of low infectivity, that progress was now satisfactory, and that it was perfectly in order for him to continue at school.

The scheme was put into operation in February, 1951, and a careful note made of the school from which any subsequent case came and also of the subtype of *M. canis* involved.

Results

The results of the experiment are set out in Table I. By studying the type of organism, the time lapse between cases, and the school involved, it was possible to determine whether the infection had been propagated to another child. In fact, not one case of direct infection followed the return to school of any of the 24 children. It would have been well within the bounds of possibility for coincidental infections with the same type to occur in a school, but even this seems not to have taken place during the period under review.

Case 14 attended the same school group as Cases 9 and 10, but a different organism was involved. Case 25 was in the same school group as Cases 15 and 19, but none of these children was infected at the same time. No new case in a schoolchild has been reported in Newport for four months.

Discussion

The main consideration in scalp ringworm is the loss of schooling brought about, especially in the scholarship year. With the common childish complaints, such as the acute specific fevers, the period of absence usually is only a matter of weeks, but with ringworm it may be a matter of months. Efforts to avoid this loss of tuition merit serious attention. In localities where *M. canis* is the exclusive dermatophyte there need be no interruption in school attendance because of ringworm.

The possibility of allowing children with active ringworm to attend school has been raised before. In the annual reports of the Chief Medical Officer of the Board of Education (1927, 1933) it is stated that in rural areas where *x* rays are not available the child's hair must be clipped short, appropriate ointment applied, and a linen cap worn, and in such circumstances affected children may be allowed to attend school. No distinction in types of cases is made here, and, from my survey, little use has been made of this concession, particularly as *x* rays have become more generally available. Whether it would be profitable to allow *M. audouini* cases in school is a matter of conjecture and one which is being pursued.

It is not possible to calculate accurately the number of cases of *M. canis* ringworm excluded from school in one year, but the figure must be high. Apart from the question of contagion, with which I have dealt, there can be no objection to these children being in school, because no subjective illness is produced in ringworm. The risk of child-to-child contagion is slight anyway, and it is virtually impossible if simple precautions are taken.

Summary

The importance and methods of distinguishing between *M. canis* and *M. audouini* scalp ringworm are indicated.

Some epidemiological considerations regarding *M. canis* ringworm are presented.

The role of microsporum ringworm as a cause of loss of schooling is discussed.

The results of a survey of the incidence of ringworm in the areas of the major education authorities of England and Wales are tabulated and analysed.

An experiment, carried out in Newport, where the scalp ringworm is almost exclusively of the *M. canis* type, and in Monmouthshire is described. Twenty-four children were allowed to continue at 19 schools, the exclusion rule being waived. In no case was the infection propagated.

The conclusion is reached that children with *M. canis* ringworm should neither be treated by *x*-ray epilation nor be excluded from school.

My thanks are due to Dr. David Lawrence, medical officer of health for Newport, for permitting me to carry out this investigation and for co-operating so helpfully. Also to Dr. Jacqueline Walker, of the Department of Medical Mycology, London School of Tropical Medicine and Hygiene, for carrying out the culture and identification of the fungi.

REFERENCES

Beare, J. Martin, and Cheeseman, E. A. (1951). *Brit. J. Derm.*, 63, 165.
Carslaw, R. W. (1951). Ibid., 63, 18.
Chief Medical Officer, Board of Education (1927). Annual Report, p. 166. London.
—— (1933). Ibid., p. 88.
Dixon, H. M. (1948). Annual Report of Principal School Medical Officer, Newcastle-upon-Tyne, p. 21.
Duncan, J. T. (1948). In *Modern Trends in Dermatology*, p. 221, edited by R. M. B. MacKenna. Butterworth, London.
Roberts, L. (1909). *Brit. J. Derm.*, 21, 72.
Sharp, H. (1951). *Aust. J. Derm.*, 1, 138.
Thomas, B. A., Lennox, M., and Duncan, J. T. (1945). *British Medical Journal*, 2, 346.
Walker, J. (1950). *Brit. J. Derm.*, 62, 239.

FIELD TRIALS OF NEW ANTIMALARIALS IN WEST AFRICA

BY

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AND

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The value of new antimalarials has not always been assessed in the field in comparison with other similar drugs, and specific claims for one or another of the new compounds are difficult to judge when each has had only a limited number of clinical tests. Differences which are known to exist between geographical strains of malaria parasites justify comparative field trials in many tropical areas.

The present difficulties in carrying out chemotherapeutic tests of new compounds in temperate climates on cases of induced malaria and/or on non-immune volunteers increase the value of properly designed field trials in areas where indigenous malaria is common.

There has been little investigation, especially in tropical Africa, of the value of "camoquin" and pyrimethamine ("daraprim") in comparison with older antimalarials. The present paper reports on results of a chemotherapeutic trial of these drugs and of two other antimalarials, chloroquine sulphate ("nivaquine") and a new compound of the acridine series named "azacrin."

This last drug is a 2-methoxy-6-chloro-9-(5′-diethylamino-2′-pentyl) amino-3-aza-acridine dihydrochloride synthesized recently by Messrs. Ward, Blenkinsop and Co. jointly with Messrs. Howards and Sons, Ltd. The first laboratory tests against *Plasmodium gallinaceum* in chicks and *P. berghei* in mice have shown that this compound, given by the mouth, possesses good schizonticidal activity at a dose of 25 mg./kg. in chicks and at a dose of 5 mg./kg. in mice. Its toxicity for experimental animals was found to be low. No data on toxicity of this drug to man being hitherto available, it was taken as a precautionary measure by one of us before using it in field trials on children. The daily dose of 0.4 g. taken for five days having produced only minor side-effects (nausea), it was decided to use this drug for a field trial.

Present Investigation

The method of investigation was that developed by one of us (Bruce-Chwatt, 1951) and subsequently used in the first field trials of pyrimethamine (Archibald, 1951). This method is based on a preliminary selection of an adequate group of African schoolchildren, 5–10 years of age, all naturally infected with malaria. After the administration of a suitable therapeutic dose of the drug to be tested, daily blood examinations of each child are carried out. The parasite rate, parasite density, and any other malariometrical indices are calculated for each group from the results of daily examinations.

Blood slides (thin and thick film) were stained with Giemsa, and parasite rates and counts were based on the examination of thick films. Parasite counts were made from the parasite leucocyte ratio, and the number of parasites per c.mm. was calculated. No film was declared negative before the examination of at least 200 thick-film fields. Parasite density indices were computed as previously described (Bruce-Chwatt, 1951). The speed of decrease of the initial 100% parasitaemia of each group to the lowest level was used as a criterion of the comparative therapeutic activity of the investigated drug against the specific parasite.

For the purpose of the present trial 120 schoolchildren 5–10 years of age were selected after a preliminary investigation and divided into five groups. The first four groups were treated with chloroquine sulphate, pyrimethamine, camoquin and azacrin respectively. The fifth group was not given any drug and represented the control. The administration of each drug was invariably made under our personal supervision.

In the chloroquine sulphate group the drug was given in two different regimens. One-half received 0.75 g. (3 tablets) in a single dose on D day; the other half received 0.75 g. (three 0.25-g. tablets) on D day as a single dose, followed by 0.25 g. (1 tablet) on each of the two following days. In terms of chloroquine base the total dosage was 0.45 g. and 0.75 g. respectively.

The pyrimethamine group also received two different dosages of the drug. One-half had a single dose of 25 mg. (1 tablet) on D day, and the other half had 25 mg. on D day followed by the same dose on the next day. The camoquin group received one dosage only—0.4 g. (2 tablets) as a single dose on D day. The azacrin group was given 0.2 g. (2 tablets) on D day followed by 0.1 g. (1 tablet) on each of the two following days. The dosage of the four drugs is half the usual adult dose. The average age of the

children was 7.6 years. Apart from the preliminary selective examination every child was examined on D day immediately before the administration of the first dose and then on days D+1, D+2, D+3, D+4, D+7, and D+10. The results of the trial are shown in the Table.

Results of Comparative Field Trials of Four Antimalarial Drugs

Group and Day	No. of Cases	*P. falciparum*					*P. malariae*	
		Trophozoites			Gametocytes			
		No.	%	Density Index	No.	%	No.	%
Chloroquine sulphate I (0·75 g. single dose):								
D	15	15	100	3·14 (47/15)	0	0	4	26·6
D+1 ..	13	11	84·5	1·62 (21/13)	2	15·4	0	0
D+2 ..	15	0	0	0 0	4	26·6	1	6·7
D+3 ..	15	0	0	0 0	2	13·3	0	0
D+4 ..	14	0	0	0 0	1	7·2	0	0
D+7 ..	12	0	0	0 0	1	8·3	0	0
D+10 ..	13	0	0	0 0	2	15·4	0	0
Chloroquine sulphate II (1·25 g. in 3 days):								
D	18	18	100	3·00 (54/18)	1	5·6	1	5·6
D+1 ..	18	14	77·8	1·95 (35/18)	0	0	0	0
D+2 ..	18	3	16·7	0·33 (6/18)	1	5·6	0	0
D+3 ..	18	0	0	0 0	3	16·7	0	0
D+4 ..	16	0	0	0 0	1	6·2	0	0
D+7 ..	17	0	0	0 0	1	5·9	0	0
D+10 ..	16	0	0	0 0	3	18·7	0	0
Pyrimethamine I (25 mg. single dose):								
D	15	15	100	2·81 (42/15)	1	6·7	1	6·7
D+1 ..	15	10	66·5	1·67 (28/15)	0	0	0	0
D+2 ..	14	1	7·1	0·07 (1/14)	3	21·4	2	13·4
D+3 ..	15	0	0	0 0	3	20·0	0	0
D+4 ..	13	0	0	0 0	4	30·8	0	0
D+7 ..	14	0	0	0 0	5	35·7	0	0
D+10 ..	14	0	0	0 0	4	28·5	0	0
Pyrimethamine II (50 mg. in 2 days):								
D	17	17	100	3·70 (63/17)	1	5·9	2	11·7
D+1 ..	17	12	70·5	2·12 (36/17)	3	17·6	2	11·7
D+2 ..	17	1	5·9	0·06 (1/17)	5	29·5	1	5·9
D+3 ..	17	0	0	0 0	2	11·7	0	0
D+4 ..	16	0	0	0 0	6	37·4	0	0
D+7 ..	15	0	0	0 0	2	13·3	0	0
D+10 ..	15	0	0	0 0	4	26·6	0	0
Camoquin (0·4 g. single dose):								
D	28	28	100	3·2 (90/28)	5	17·8	3	11·7
D+1 ..	23	15	65·0	1·52 (35/23)	2	8·7	1	44·0
D+2 ..	27	1	3·7	0·04 (1/27)	6	22·2	0	0
D+3 ..	26	0	0	0 0	5	19·3	0	0
D+4 ..	27	0	0	0 0	6	22·2	0	0
D+7 ..	27	0	0	0 0	4	14·8	0	0
D+10 ..	27	0	0	0 0	4	14·8	0	0
Azacrin (0·4 g. in 3 days)								
D	12	12	100	3·8 (44/12)	4	33·3	1	0·09
D+1 ..	11	6	54·5	1·0 (11/11)	2	18·2	1	0·09
D+2 ..	12	1	8·3	0·08 (1/12)	4	33·3	1	0·09
D+3 ..	11	0	0	0 0	2	18·2	1	0·09
D+4 ..	5	0	0	0 0	2	40·0	0	0
D+7 ..	10	0	0	0 0	3	30·0	0	0
D+10 ..	11	0	0	0 0	3	27·3	0	0
Control:								
D	15	15	100	2·8 (42/15)	2	13·3	1	6·6
D+1 ..	14	11	78·2	2·7 (30/11)	1	7·1	1	7·1
D+2 ..	15	14	93·0	2·6 (37/14)	2	13·3	1	6·6
D+3 ..	14	11	78·2	2·0 (22/11)	2	14·2	1	7·1
D+4 ..	11	11	100	1·49 (16/11)	3	27·2	0	0
D+7 ..	13	10	77·8	2·1 (21/10)	2	15·4	1	7·7
D+10 ..	13	13	100	2·2 (29/13)	2	15·4	2	15·4

Discussion

These results show that all four drugs are very good schizonticides for *P. falciparum*. There seems to be relatively little difference between the speed with which in a selected group of African children each drug reduces the parasite rate for trophozoites of *P. falciparum* from 100% to 0 (clearance time).

The comparative clearance time of trophozoites of *P. falciparum* in each of the tested six groups was found to be as follows: chloroquine sulphate (dosage I), 1.78±0.41 days; chloroquine sulphate (dosage II), 1.95±0.39 days; pyrimethamine (dosage I), 1.74±0.26 days; pyrimethamine (dosage II), 1.77±0.24 days; camoquin, 1.69±0.43 days; azacrin, 1.58±0.42 days.

The clearance time found in this investigation for chloroquine is very close to the 1.80 days found for this drug in one of our first trials (Bruce-Chwatt, 1951). It was thought at first that the clearance time obtained in this type of trial with chloroquine is longer by about half a day when compared with figures quoted by investigators whose reports were based on clinical trials in East Africa (Handfield-Jones, 1949), in Tunisia (Durand, Schneider, and Dupoux, 1949), in Indo-China (Canet, 1950). Our average figures for the chloroquine clearance time of asexual parasitaemia due to *P. falciparum* are, however, almost identical with 1.84 days reported from India by Chaudhuri, Chakravarty, Rai Chaudhuri, and Poti (1952), and very close to 2 days observed by Singh and Kalyanum (1952).

In our present investigation camoquin appeared to have a faster action than any of the other drugs, except azacrin. This was somewhat unexpected, since in Bertagna's (1951) summary of information on camoquin the reported clearance time of asexual parasitaemia due to *P. falciparum* had a range between 24 and 120 hours, with an average duration of 53 hours, or 2.25 days. This is also the figure reported more recently by Mein (1951) from Brazil.

The camoquin clearance time of *P. falciparum* parasitaemia observed by us is slightly longer than 1.25 days reported by Hoekenga (1951) from Honduras, 1.2–1.4 days found in Bolivia (Villarejos, 1951), or 1.4–1.6 days reported by Singh and Kalyanum (1952) from India.

The clearance time for *P. falciparum* obtained with pyrimethamine is 1.74 days. This is close to the results obtained by the French workers in Tunisia (1.25 days) and in Indo-China (1.56 days) (Schneider, Canet, and Dupoux, 1952). In the Gambia, however, work by McGregor and Smith (1952) produced slower clearance times in cases of clinical *P. falciparum* malaria treated with pyrimethamine in doses different from those used in the present investigation. The clearance time in infants treated by them with an average dose of 2–4 mg. was 2.82 days even when two infants who failed to respond to therapy are excepted. In a similar series of young children it was 2.57 days, and in a small series of adults, it was 2.25 days.

None of the four antimalarials is an effective direct gametocide for *P. falciparum*, since the crescents persist in the peripheral blood for at least 10 days after the administration of the drugs and show no obvious and constant morphological changes.

In the camoquin series, in which gametocytes of *P. falciparum* were already present in the blood, there was little evidence of any gametocidal action. The observation supports the results quoted by Bertagna (1951) and by Mein (1951), and is in marked contrast to the findings of Singh and Kalyanum (1952), who found that 40% of their crescent carriers were cleared within six days.

Infections with *P. malariae* were too few and of a generally too-low density to obtain series of malariometrical data comparable with series of *P. falciparum*. Nevertheless it seems that chloroquine and camoquin have a more marked action on *P. malariae* (clearance time 1.2–1.3 days) than either pyrimethamine or azacrin (clearance time 2 days and 3 days respectively).

Two infections with *P. ovale* mixed with *P. falciparum* disappeared within 24 hours after the administration of camoquin and azacrin.

Of the four drugs used in the present trial pyrimethamine was tolerated best and no complaints of headache, nausea, or vomiting were made by any children who took it.

Chloroquine sulphate was also well tolerated, though two children complained of nausea after taking a single dose of three tablets. Four children out of 23 given camoquin complained of headache and nausea within four hours of taking 0.4 g. Azacrin was well tolerated in a single dose of two tablets (0.2 g.), but three tablets caused nausea, pain in the stomach, and vomiting in 7 out of 10 children.

It must be emphasized however, that some children had had little or no food in the morning when the drugs were administered and that the side-effects noted might have been less frequent if the drugs had been given after a meal.

Summary

Field trials with chloroquine sulphate, pyrimethamine, camoquin, and azacrin (an amino-aza-acridine) were carried out on 120 African schoolchildren with a subclinical natural infection with *P. falciparum* and *P. malariae*.

All four antimalarials have proved to be good schizonticides. The clearance time of parasitaemia due to trophozoites of *P. falciparum* was shortest with azacrin (1.58 days) and camoquin (1.69 days), closely followed by pyrimethamine (1.84 or 1.77 days) and chloroquine sulphate (1.78 or 1.95 days). None of the four drugs shows any direct gametocidal action.

It appears that chloroquine sulphate and camoquin have a more marked action on *P. malariae* than either pyrimethamine or azacrin.

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REFERENCES

Archibald, H. M. (1951). *British Medical Journal*, **2**, 821.
Bertagna, P. (1951). *Bull. Wld Hlth Org.*, **4**, 267.
Bruce-Chwatt, L. J. (1951). *Trans. roy. Soc. trop. Med. Hyg.*, **44**, 563.
Canet, J. (1950). *Bull. Soc. Path. exot.*, **43**, 538.
Chaudhuri, R. N., Chakravarty, N. K., Rai Chaudhuri, M. N., and Poti, S. J. (1952). *British Medical Journal*, **1**, 568.
Durand, P., Schneider, J., and Dupoux, R. (1949). *Bull. Soc. Path. exot.*, **42**, 549.
Handfield-Jones, R. P. C. (1949). *Ann. trop. Med. Parasit.*, **43**, 345.
Hoekenga, M. T. (1951). *Amer. J. trop. Med.*, **31**, 139.
McGregor, I. A., and Smith, D. A. (1952). *British Medical Journal*, **1**, 730.
Mein, R. M. (1951). *Amer. J. trop. Med.*, **31**, 212.
Schneider, J., Canet, J., and Dupoux, R. (1952). *Bull. Soc. Path. exot.*, **45**, 33.
Singh, I., and Kalyanum, T. S. (1952). *British Medical Journal*, **2**, 312.
Symposium on Daraprim (1952). *Trans. roy. Soc. trop. Med.*, **46**, 465.
Villarejos, V. M. M. (1951). *Amer. J. trop. Med.*, **31**, 703.
W.H.O. (1951). Technical Report Series, No. 38. Geneva.

AN ASSESSMENT OF CHLOROPHYLL AS A DEODORANT

BY

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Between 1943 and 1950 many claims were made in published articles for the beneficial effect of water-soluble chlorophyll in stimulating the growth of granulation tissue and accelerating epithelization of skin ulcers. The work of Moss and his colleagues (1949) cast doubt on the validity of these claims. In 1951 the Council on Pharmacy and Chemistry of the American Medical Association could find no evidence that water-soluble chlorophyll stimulated granulation and healing beyond the normal rate.

Many reports also noted a deodorant property in chlorophyll when applied to skin ulcers. More recent workers have claimed that the alleged deodorant action of chlorophyll is effective against all kinds of body smells when the substance is taken orally. Such claims have received the widest publicity in the lay press. On the other hand, the *Journal of the American Medical Association* (1951) questions whether chlorophyll does in fact have deodorant properties at all.

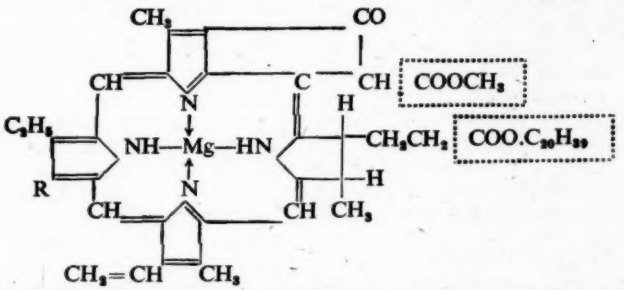
The present communication presents the results of a number of *in vitro* experiments designed to determine the effect of chlorophyll on a number of odours. Some clinical experiences with the drug are also recounted.

Full summaries of the earlier work with chlorophyll have appeared in recent leading articles in the *British Medical Journal* (1952) and the *Lancet* (1952). It is therefore unnecessary to review the literature again here. It may be noted, however, that all published findings of the action of chlorophyll as a deodorant have depended on the olfactory sense of the observer. Not only is the sense of smell notoriously inconstant from one observer to another, it is also apt to fluctuate in the one observer in different circumstances. Of all the human senses the sense of smell is the most easily affected by suggestion.

Chemistry

As there are various types of chlorophyll, a brief comment is required on the chemical composition of the substance used in these experiments.

Chlorophyll is extracted from plants (especially nettles, spinach, and alfalfa) with alcohol or acetone. This substance, which has the formula shown below, is oil-soluble



Chlorophyll formula. R = CH_3 (chlorophyll-*a*) or CHO (chlorophyll-*b*). Ester groups indicated by dotted boxes.

but not water-soluble. It has been described (*Lancet*, 1952) as "a system of four pyrrole rings pivoted on a central magnesium atom," and the formula is similar to that of haem, in which the pyrrole rings pivot in similar manner on an iron atom. Treatment of this substance with acid removes the magnesium atom. The magnesium atom is also easily displaced by other metals—for example, copper.

Treatment with alkali (hydrolysis) splits off the two ester groups shown in the diagram. The resulting substance is a salt of the dicarboxylic acid chlorophyllin. The sodium and potassium salts of this acid are soluble in water and constitute the active principles of the so-called water-soluble chlorophylls (Mitchell, 1952). The therapeutic substance called chloresium was defined by the Council on Pharmacy and Chemistry (1951) as consisting chiefly of the copper complex of the sodium and potassium salts of chlorophyllin. This is the substance used in those published trials in which the nature of the chlorophyll was disclosed. More often, proprietary preparations were used and no information was supplied about their chemical composition.

In the present experiments the substance hereafter called chlorophyll solution A consists chiefly of sodium copper chlorophyllin, and is made up in a solution containing 1 g. in 10 ml. The substance called chlorophyil solution B is a crude commercial preparation of water-soluble chlorophyll intended for use as colouring matter. Solution C is a proprietary preparation intended for use as an atmospheric deodorant, and is exposed to the atmosphere by means of a wick. Solution D is a proprietary water-soluble preparation sold for dispensing purposes. It is reported to contain 12.5% water-soluble chlorophyll.

Experiments

The principle of the first experiments is the same as that used by Alstead (1942) in assessing the deodorant properties of activated carbon. Methylmercaptan gas (one of the substances contributing to the odour of the gas normally present in the lower bowel) is evolved by adding 5N solution of

sodium hydroxide to crystals of thiourea sulphate (Fig. 1). To obtain as near standard conditions as possible in consecutive experiments, constant quantities of the reagents are used (3.5 g. of thiourea sulphate and 5 ml. of 5N NaOH). The flask containing the reagent is kept in a water-bath at a constant temperature of 65° C. Nitrogen is bubbled through the flask at a constant rate of flow so that the inert gas carries mercaptan through the rest of the apparatus. The gas passes through two bell-jars, securely clamped together, where it comes into intimate contact with a screen of filter paper soaked in chlorophyll solution. The filter paper is arranged around a baffle (Fig. 1).

After passing through this part of the circuit the gas bubbles through test-tubes containing N/10 solution of iodine. Any mercaptan passing over combines with iodine to form colourless hydriodic acid. Thus the time taken to decolorize a standard quantity of iodine solution can be used as a measure of the amount of mercaptan passing over. Alternatively, after some, but not all, of the iodine has combined with mercaptan, a back-titration with N/10 sodium thiosulphate solution indicates the amount of iodine remaining unchanged, and by difference the amount of mercaptan which has reacted with the iodine solution.

Experiment 1

The circuit was set up as in Fig. 1. To the filter paper around the baffle was added 2 ml. of either water or chlorophyll solution A. The whole circuit was filled with mercaptan. New reagents were then added for producing mercaptan. The iodine indicator was added and the gas passed across the circuit for 20 minutes. In this way as nearly similar quantities of mercaptan as could be obtained were exposed to water or to chlorophyll. By back-titrations at the end of the experiment the amount of iodine which had been reduced was noted.

The results were as follows: (1) water, 2 ml. on filter paper—12.6 ml. iodine solution reduced; (2) chlorophyll 2 ml. on filter paper—14.6 ml. iodine solution reduced; and (3) chlorophyll, 2 ml. on filter paper—18.5 ml. iodine solution reduced. These findings show at once that chlorophyll has not removed or altered all the mercaptan exposed to it. Indeed, more mercaptan has passed across when exposed to chlorophyll than when exposed to water.

Experimental error is obviously too great to allow of exact quantitative comparison. The source of error was thought to lie in the existence of a large dead space resulting from the use of bell-jars, and accordingly this was eliminated in experiment 2.

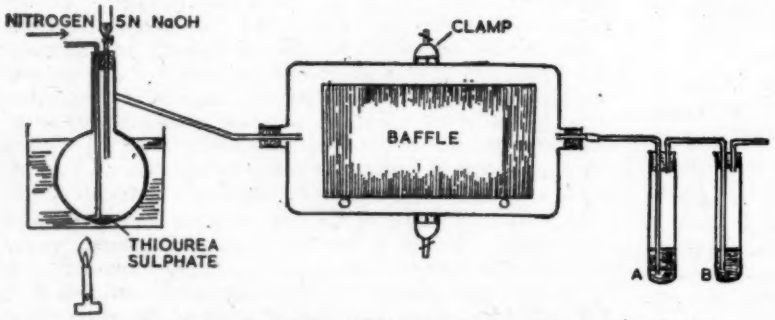


FIG. 1.—A and B=Test-tubes containing iodine, used an an indicator.

FIG. 2.—A=Test-tube containing chlorophyll solution, and used as a trap to collect froth from the burette. B=Test-tube containing iodine, used as an indicator.

Experiment 2

The apparatus is shown in Fig. 2. An ordinary 25-ml. burette is filled with the substance to be tested. It is tilted slightly off the horizontal so that bubbles of gas slowly traverse the column of fluid. The gas then passes to the test-tubes. The first test-tube, which also contains a measured volume (10 ml.) of the chlorophyll solution being tested, acts as a trap. Chlorophyll solution has a low surface tension, and bubbles of gas passing through it tend to carry the solution forward as foam. This is caught in the first test-tube. The second test-tube contains 5 ml. of iodine solution. The time taken for decolorization of successive tubes of 5 ml. of iodine is noted.

The reading from the first tube of iodine is always the highest, as mercaptan is soluble in water. The first reading is therefore a measure of the solubility of mercaptan in the solutions used. These were as follows:

Water	34 minutes
Chlorophyll solution A (*a*)	34 „
„ „ „ (*b*)	35 „
Chlorophyll solution C	36 „

After decolorization of this first tube of 5 ml. of iodine, fresh reagents for production of mercaptan were added and notes were made of the times taken to decolorize a second and then a third test-tube, each containing 5 ml. of iodine. The results obtained on two different days were as follows:

First Test.—Rate of flow of nitrogen carrying mercaptan across=8 bubbles a minute.

	Time to decolorize 5 ml. iodine
Water (i)	4 minutes
„ (ii)	6½ „
Chlorophyll solution A (i)	4 „
„ „ „ (ii)	7 „

Second Test.—Rate of flow of nitrogen=4 bubbles a minute. (N.B., reduced rate of flow.)

	Time to decolorize 5 ml. iodine
Chlorophyll solution A (i)	7½ minutes
„ „ „ (ii)	22½ „
Chlorophyll solution C (i)	6 „
„ „ „ (ii)	22 „

Thus, regarding chlorophyll solution A as a standard, it will be seen that there is no difference in the time taken for a constant amount of mercaptan gas to pass through solutions of chlorophyll A and C and water. Furthermore, the times taken for such solutions and water to become saturated with mercaptan are the same. It is obvious, therefore, that intimate exposure of mercaptan gas to the action of chlorophyll solution, as described above, did not reduce the volume of the gas.

Experiment 3

This experiment involves the use of very much smaller quantities of mercaptan and of other odorous vapours, and exposing these to chlorophyll for much longer periods. This method depends on the reliability of the observer's olfactory sense, and is open to criticism on that account. Such criticism, however, as has already been noted applies equally to all who have made positive claims for the deodorant value of chlorophyll.

The apparatus is shown in Fig. 3. The bell-jar stands on a ledge in a water-bath, so that there is a complete water seal. A is a filling funnel from which N/2 sulphuric acid is run in; B is a shallow dish containing N/2 sodium hydroxide saturated with

methylmercaptan. By mixing equal quantities of acid and base methylmercaptan gas is liberated. The filter paper (C) stands clear of the water in a petri dish soaked with chlorophyll or other substance under trial.

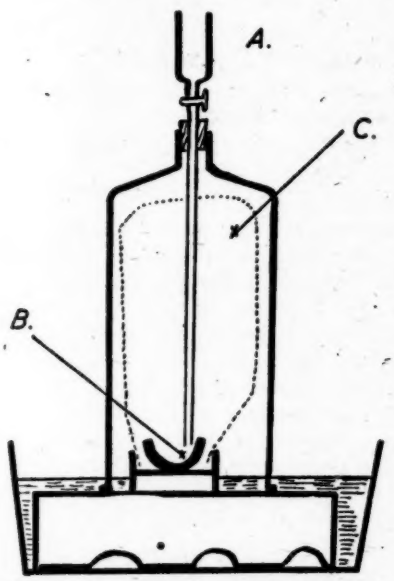


FIG. 3.—A = Filling funnel (N/2 H_2SO_4). B = Dish containing mercaptan in N/2 NaOH. C = Filter paper soaked in chlorophyll.

The experiment is set up and stands for one to three days. The bell-jar is then opened and the odour of its contents noted. No attempt is made to record the *degree* of smell present, as the method is too subjective to provide reliable quantitative results. The smell is therefore merely recorded as being present or absent.

These experiments were also carried out using (*a*) ether, and (*b*) syrup of garlic to yield characteristic smells.

The results are shown in the Table. One millilitre of N/2 NaOH when neutralized with acid liberates very approximately 30 mg. of methyl mercaptan, or 130 ml. of the gas. In two cases tablets of chlorophyll, marketed for oral use, were crushed and suspended in water (one tablet per ml.), and this suspension was exposed to the gas.

Source of Smell	Substance under Trial	Quantity	Duration of Exposure	Result
Methylmercaptan:				(Smell +/−)
30 mg. ..	Water (control)	3 ml.	12 hours	+
30 ,, ..	,, ,,	3 ,,	13 ,,	+
30 ,, ..	Chlorophyll solution A	2 ,,	12 ,,	+
30 ,, ..	,, ,, ,,	3 ,,	12 ,,	+
30 ,, ..	,, ,, ,,	3 ,,	14 ,,	+
30 ,, ..	,, ,, ,,	3 ,,	16 ,,	+
15 ,, ..	Water (control)	3 ,,	14 ,,	+
15 ,, ..	Chlorophyll solution A	3 ,,	14 ,,	+
15 ,, ..	,, ,, ,,	3 ,,	15 ,,	+
15 ,, ..	Suspension of chlorophyll tablets	3 ,,	12 ,,	+
15 ,, ..	,, ,, ,,	5 ,,	20 ,,	+
15 ,, ..	Water	5 ,,	20 ,,	+
15 ,, ..	Chlorophyll solution A	5 ,,	22 ,,	+
15 ,, ..	,, ,, ,,	2 ,,	46 ,,	−*
15 ,, ..	,, ,, ,,	1·5 ,,	46 ,,	+
Meth-ether:				
4 ml. ..	Water	2 ,,	28 ,,	+
2 ,, ..	Chlorophyll solution A	0·5 ,,	22 ,,	+
1 ,, ..	,, ,, ,,	4 ,,	47 ,,	+
1 ,, ..	,, ,, D	4 ,,	25 ,,	+
1 ,, ..	,, ,, ,,	4 ,,	36 ,,	+
Syrup of garlic:				
5 ml. ..	Water	1 ,,	12 ,,	+
5 ,, ..	Chlorophyll solution A	1 ,,	12 ,,	+

* In this case the smell of mercaptan was not detected. There was, however, a very strong smell of chlorophyll, which may have masked it.

This experiment, which involved exposure of small quantities of mercaptan, ether, and syrup of garlic in a small enclosed space for long periods of time to filter paper soaked in various chlorophyll preparations, showed a possible complete deodorant effect in only one case, and because of the presence of a strong smell of chlorophyll on that occasion it can hardly be regarded as being significant. It is concluded from this experiment that chlorophyll when exposed in this way to an odour does not remove the odour from the air.

Experiment 4

(*a*) Three jars were set up containing, respectively, 4 ml. of concentrated solution of chlorophyll; 4 ml. of dilute solution of chlorophyll; and 4 ml. of water. To each was added one drop of perfume. On smelling the jars subsequently no difference could be detected between them. In each case all the liquid evaporated within 14 days. The smell of the perfume persisted strongly in all the jars even after five months. A similar experiment, using slices of onion instead of perfume, showed no difference after 24 hours. The smell was so offensive that the experiment then had to be abandoned.

(*b*) Stoppered test-tubes containing 10 ml. respectively of water, chlorophyll solution A, and solution C were set up for 72 hours, with 10 ml. of a solution of mercaptan in water added to each. At the end of this time there was a strong smell of mercaptan from each tube. It was also noted that the tube containing solution C (a preparation of chlorophyll which is perfumed) yielded the smell of mercaptan after standing for 72 hours, but on being shaken the smell of the perfume emerged and masked the smell of mercaptan fairly effectively. This was noted on several occasions, and suggests that the apparent deodorant property of such a preparation is due to substitution of a smell which is stronger but more pleasant than that which it is desired to eliminate. This experiment was repeated, using a smaller quantity (1 ml.) of mercaptan solution. Instead of adding chlorophyll solutions, however, plugs of cotton-wool were inserted at the upper part of each tube. These were then saturated respectively with (1) chlorophyll solution A; (2) chlorophyll solution A evaporated to dryness; (3) powdered activated carbon; and (4) a control of plain cotton-wool. After 24 hours the smell of mercaptan was perceptible in all the tubes. After a further 24 hours the smell was perceptible from all tubes except that containing activated carbon.

(*c*) A series of four stoppered test-tubes was set up containing (1) 5 ml. of syrup of garlic and 4 ml. of chlorophyll solution A; (2) 5 ml. of syrup of garlic and 4 ml. of chlorophyll solution D; (3) 5 ml. of syrup of garlic alone; and (4) 5 ml. of chlorophyll solution A alone. The smell of garlic was present in all tubes except the fourth whenever the contents were smelled—at intervals from one day to one month after setting up. (The test-tubes were left in an ordinary warm room during all this time.)

Clinical Trial

The following simple *in vivo* tests were performed:

(*a*) A patient incontinent of urine and faeces was being nursed in a special bed which gathered the excreta direct into a receptacle. This patient was given three-day courses of (1) chlorophyll solution A, 400 mg. daily; (2) proprietary chlorophyll tablets, 400 mg. daily; and (3) periods with no chlorophyll. The days on which particular courses were given were not known to the observer. Each morning the odour of the receptacle containing the night's collection of urine was noted. This characteristic and unpleasant odour of urine was present every day no matter whether chlorophyll was being given or not.

(*b*) *Asparagus Test.*—It is well known that in many people the urine develops a characteristic odour within an hour or two of eating asparagus. One of the earliest and widely quoted observations on the alleged deodorant action of chlorophyll is one by Westcott (1950), who stated that oral administration of chlorophyll before taking asparagus prevented the appearance of this odour in the urine. A colleague in this hospital who consistently detects the asparagus odour in his urine after eating this vegetable decided to test Westcott's findings. In the 24 hours preceding the meal he swallowed 48 100-mg. tablets of a proprietary water-soluble chlorophyll in doses of 6–12 tablets at intervals of four hours. He then took his meal, which included an average serving of asparagus. Some two hours later the urine which he passed smelled strongly of the volatile substances of asparagus, and the odour was readily

detected in further specimens of urine passed about 12 hours later. It is concluded that, in this observer, chlorophyll in doses at least 25 times greater than those usually recommended was valueless in preventing the characteristic smell of the urine following ingestion of asparagus. It was also noted that the smell of the faeces was unaffected by this large dose of chlorophyll.

I have confirmed these findings in similar manner, and have also found that the oral administration of 800 mg. of chlorophyll daily for a week did not remove the odour of urine, faeces, or axillary perspiration.

So much has been made of the alleged deodorant effect of chlorophyll on the urine of persons who have eaten asparagus that it would be helpful if a large number of doctors would themselves repeat this simple experiment. The experience would be in the best tradition of the advice offered to Jenner by John Hunter.

Conclusions

Exposure of methylmercaptan gas in a closed system to water-soluble chlorophyll did not reduce the amount of gas passing over to an indicator, compared with a control.

Exposure of small quantities of methylmercaptan gas to water-soluble chlorophyll in a closed system for up to three days did not remove the smell of mercaptan.

Mixtures of water-soluble chlorophyll and various strong-smelling solutions did not remove the smell of these solutions even after exposure for one or more months.

Clinical trials are reported in which the smell of urine, faeces, sweat, and of urine after ingestion of asparagus was not removed after taking large numbers of chlorophyll tablets.

I should like to thank Professor J. W. Cook, F.R.S., for the use of many facilities in the Department of Chemistry, University of Glasgow, also Professor Stanley Alstead and Dr. D. Gibson for many helpful suggestions.

REFERENCES

Alstead, S. (1942). *Lancet*, **1**, 669.
British Medical Journal, 1952, **2**, 1086.
Council on Pharmacy and Chemistry of the American Medical Association (1951). *J. Amer. med. Ass.*, **146**, 34.
J. Amer. med. Ass., 1951, **147**, 99
Lancet, 1952, **2**, 372.
Mitchell, W. (1952). *Retail Chem.*, **23**, 27, 65.
Moss, N. H., Morrow, B. A., Long, R. C., and Ravdin, I. S. (1949). *J. Amer. med. Ass.*, **140**, 1336.
Westcott, F. H. (1950). *N.Y. St. J. Med.*, **50**, 698.

The Faculty of Ophthalmologists has for some time been considering the desirability of standardizing reading types used for testing vision. Suggestions from many sources have been studied and the final recommendations of the Council of the Faculty have been embodied in a memorandum by Mr. F. W. Law (*Brit. J. Ophthal.*, 1952, **36**, 689). The Council's recommendations for a standard test of near vision are that: (1) "Times Roman" type shall be used, with "standard" spacing; (2) suitable passages of literature shall be selected, and a different passage used for each type; (3) specimens of printing in 5, 6, 8, 10, 12, 14, 18, 24, 36, and 48 point type shall be used, starting with the smallest [1 point = 1/72 in.]; (4) a few isolated words in lower-case letters shall be printed in each size; (5) near acuity shall be recorded by the letter N, followed by a number indicating type-face size—for example, N.5, N.8, etc.; (6) the test shall include a facsimile of a Snellen distance chart reduced to 1/17 normal size and used at 35 cm. distance, the result being recorded as a "Snellen equivalent"—for example, N = 6/9; (7) the test may also include reproductions or actual portions of familiar types in everyday use; (8) near test types shall be reproduced on sheets about 9 × 6 in. (23 × 15 cm.); (9) the print shall be on dead-white matt-surface cartridge paper or board, and the latter may be varnished to increase durability.

CAPACITY OF A CATIONIC EXCHANGE RESIN ("ZEO-KARB 225") IN VIVO

BY

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With the technical assistance of ALISON SHEPHERD and BARBARA SEIBERT

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Cationic exchange resins are insoluble powders which will exchange cations on the same principle as the familiar water softeners. The exchange obeys the law of mass action, and mixtures of cations combine with the resin *in vitro* in proportions determined by equilibrium constants (MacIntyre and Jordan, 1951). *In vitro* the affinity for monovalent ions follows the order $K > Na > NH_4 > H$. The affinity for divalent ions is greater than for monovalent ions. The resins have been given in the H or NH_4 form to prevent absorption of Na from the bowel in patients with oedema or ascites and in patients with hypertension (McChesney, Dock, and Tainter, 1951; Greenman and others, 1951). The resins give off H or NH_4 in exchange for Na; H or NH_4 is absorbed combined with acid, and Na is excreted in the faeces combined with resin. The resin takes up K and other cations as well, and the depletion of cations may result in acidosis. To minimize these complications the resin has been given partly combined with K.

Most of the information available is on the effects of carboxylic exchange resins. In the course of work on experimental depletion of potassium we have obtained data on the effects of a sulphonated polystyrene resin, "zeo-karb 225," on the absorption of K, Na, Mg, Ca, and P with a normal diet in man. Though these data are incidental to another investigation and give information of limited scope, we think it may be useful to report them now that a pharmaceutical preparation of zeo-karb 225 has become available ("katonium"). Additional information was derived from studies of three patients who were receiving only small amounts of sodium in their diet.

Procedure

There were three experiments—F.1, W., and F.2—on two normal subjects, F. and W. The H form of the resin was given in F.1 and the NH_4 form in W. and F.2. The dose of resin was 60 g. daily for eight days, followed by 90 g. daily for eight days in F.1 and F.2 and 90 g. daily for four days in W. (These doses are two or three times what is likely to be given therapeutically.) The diets contained, per day, Na, 180–220 mEq; K, 31–38 mEq; Mg, 12–22 mEq. The composition of the diet in each experiment was constant. Resin was given with meals; added sodium was given between meals. The faecal excretion of N, P, Ca, K, Na, and Mg and the urinary acidity and ammonia were measured. Other details are available in a previous publication (Fourman, 1952).

In addition three patients were studied: a woman (A.) with intractable cardiac oedema; a man (M.) with cirrhosis of the liver, ascites, and oedema; and a woman (P.) with hypertension but without oedema or other evidence of heart failure. The patients received resin in a dose of 20, 30, or 45 g. daily while taking a diet which contained less than 20 mEq of Na a day. The faecal excretion of Na was measured in periods of seven or twelve days while the resin was given in the NH_4 form and also while it was

TABLE I.—*Effect of Resin on Daily Faecal Loss of Cations (mEq) in Consecutive Periods of Four Days*

Form of Resin:	H				NH_4							
Experiment:	F.1				W.				F.2			
Cation:	Na	K	Mg	Sum	Na	K	Mg	Sum	Na	K	Mg	Sum
Period:												
Control ..	8·2	9·9	2·4	20	5·4	7·2	5·7	18*	3·2	5·5	6·4	15·1
	8·8	8·6	6·9	24					7·4	8·9	12·1	28·4
									6·0	6·5	7·6	20·1
Resin, 60 g.	103	40·9	5·7	150	106	72·2	10·8	189*	126	61·1	11·3	198
	121	51·2	15·9	188					132	56·3	12·0	200
,, 90 ,,	139	47·6	12·3	199	169	78·6	10·3	258	149	64·3	9·0	222
	156	63·3	15·9	235	—	—	—	—	192	88·5	17·8	298
Recovery ..	21·2	17·6	24·7	64					26·9	21·2	9·6	58
	8·3	9·7	12·8	31					13·8	9·1	12·1	35
									3·1	7·9	18·5	30
Diet ..	223	38	22		212	36	12		181	31	13	

* Eight-day period.

given in the NH_4 form with K salts added to the treatment or in the K form as prepared in the laboratory. Potassium salts were given between doses of resin and not with resin.

Effect of Resin on Different Ions

In the experiments the resin took up Na, K, and Mg (Table I), but not Ca (Table II). Absorption of phosphate was possibly enhanced (Table II).

The proportions of Na, K, and Mg in the faeces were remarkably similar for the different doses of resin and in the different experiments (Table III). The mean ratio of Na:K:Mg was approximately 11:5:1. It seems likely that these proportions represented an equilibrium mixture of Na, K, and Mg for the diet provided, where the intake of Na was liberal. The amount of Na taken up by the NH_4 resin was about 2 mEq/g. and slightly more than twice that of K. The uptake of K exceeded the dietary intake. The amount of Mg taken up was small compared with the two other ions, but constituted a large proportion of the dietary intake.

In the patients who were receiving a low intake of Na, the amount of Na taken up by the resin was small and equivalent to only 0.7 mEq/g. When K was given in addition, either as K salts or as the K form of resin, the amount of Na taken up was even smaller (Table IV). The amounts of Na taken up per g. of resin were again similar for the different doses of resin given.

The number of data is small and the agreement may be fortuitous; but the results suggest that the equilibrium between resin and Na depends on the cation content of the diet and not on the dose of resin, for the range of doses given.

TABLE II.—*Effect of Resin on Daily Faecal Loss of Ca and P (mg.) in Consecutive Periods of Four Days*

Form of Resin:	H		NH_4			
Experiment:	F.1		W.		F.2	
Cation:	Ca	P	Ca	P	Ca	P
Period:						
Control ..	720	540	1,012	544*	402	344
	574	420			845	712
					500	443
Resin, 60 g.	495	360	515	362*	472	362
	673	378			296	372
Resin, 90 g.	580	289	976	240	416	220
	454	268			588	356
Recovery ..	797	566			550	380
	881	676			776	731
					1,146	792

* Eight-day period.

TABLE III.—*Percentage of Na, K, and Mg in Faeces During Administration of Resin*

Form of Resin:	H		NH_4				
Experiment:	F.1		W.		F.2		Mean
Dose of Resin (g.):	60	90	60	90	60	90	
Na	66·3	68·0	56·1	65·5	64·8	65·3	64·3
K	27·2	25·6	38·2	30·5	29·5	29·3	30·0
Mg	6·4	6·5	5·7	4·0	5·8	5·1	5·6

TABLE IV.—*Faecal Na per g. of Resin in Patients on Low-sodium Diets*

Case	Duration of Faecal Collection	Dose of Resin	Faecal Na (mEq/g. of Resin)		Amount of Added K (mEq)
			Without K Added to Treatment	With K Added to Treatment	
M.	12 days	20 g.	—	0·25	84 (as mist. pot. cit.)
A.	7 ,,	30 ,,	0·87 0·67	0·28	90 (resin given in K form)
P.	7 ,,	45 ,,	0·73 0·59	0·16 0·18	120 (as KCl)
Mean uptake of Na (mEq) per g. of resin			0·7	0·2	

Capacity of Resin in Vivo

The capacity of the H and NH_4 forms of resin *in vitro* differs because the NH_4 form has a lower moisture content (10% as opposed to 30%). Thus, while the same weights of both forms of resin were given, the effective dose of the NH_4 form was about 130% of that of the H form. The following estimates of capacity are based on the weight of resin given.

The capacity of the H resin *in vitro* is 2.5 mEq/g. (*Lancet*, 1950). The capacity of the NH_4 resin *in vitro* was estimated as 3.3 mEq/g. (calculated from the N content, on the assumption that all the N was present as NH_4). An estimate of the capacity of the resin *in vivo* was obtained from the increase in faecal excretions of cations when resin was given. The capacity calculated in this way from data in Table I was 2.4 mEq/g. for the H form and 2.8 mEq/g. for the NH_4 form in both experiments in which this form was given. These are minimum estimates of the capacity of the two forms of resin, because some resin was excreted with cation after the marker for the end of the resin period had appeared in the faeces (cf. Table I), and because not only of the increase in faecal cation but also the cations normally present in faeces may have combined with the resin.

Another estimate of the capacity of the NH_4 resin *in vivo* was given by the change in faecal N when the NH_4 resin was given. In W. there was an increase of faecal N while the resin was given, equivalent to 0.4 mEq of NH_4 per g. of resin; this suggests that 2.9 mEq of NH_4 per g. of resin was exchanged. This estimate corresponds well with the one above of 2.8 mEq/g. In F.2 the faecal N did not increase, so that in this experiment all the NH_4, or 3.3 mEq/g. of

resin, was apparently exchanged. This estimate is higher than the one above, but it may be noted that a small error in measuring faecal N would mean a large error in the estimate of capacity. Faecal N was measured in only one of the patients (P.) receiving a diet low in Na. In her the faecal N did not increase with resin, and, moreover, the changes in faecal K were consistent with the suggestion that the total capacity was not appreciably diminished when the uptake of Na was small.

These estimates show that the capacity of the resin *in vivo* may approach the capacity *in vitro*. For the NH_4 form the capacity *in vivo* was more than 2.8 and less than 3.3 mEq/g. A figure of 3 mEq/g. provides a working approximation.

Compensatory Effects

The resin prevents absorption of fixed base, but absorption of acid radicals is not diminished, and if the resin is given in the NH_4 form the acid radicals are absorbed as NH_4 salts. NH_4 is metabolized to urea, and the excess of acid radicals is excreted by the kidney. This is achieved by an increase in the renal excretion of titratable acid and NH_4.

In our experiments the titratable acidity of the urine increased rapidly to about 40 mEq/day while the resin was given. The urinary ammonia increased more gradually up to 200 mEq/day. The change in the sum of the two was about equal to the increase in faecal loss of cations (Table V). In spite of the renal compensation, the subjects were

TABLE V.—*Urinary Acidity $+NH_4$ (mEq/day). Increase Over Control Values During Four-day Periods of Giving Resin*

Form of Resin:	H	NH_4	
Experiment:	F.1	W.	F.2
Dose of resin:			
60 g.	117	142*	144
60 ,, ...	123		182
90 ,, ...	160	218	229
90 ,, ...	186	—	270

* Eight-day period.

acidotic while taking resin: the plasma bicarbonate fell to 17, 12, and 15 mEq per litre in F.1, W, and F.2. This may have been partly because it takes some days for the renal production of NH_4 to become fully established (Sartorius, Roemmelt, and Pitts, 1949). An additional reason may have been that K was lost from the body without equivalent amounts of the corresponding anion, phosphate (Fourman and Ainley-Walker, 1952). These changes were accompanied by loss of water from the cells, manifested clinically by thirst.

Discussion

With a normal intake of Na, the capacity of zeo-karb 225 *in vivo* approached its capacity *in vitro* (cf. McChesney, 1952). Na, K, and Mg were taken up in approximately constant proportions of 11:5:1, and 1 g. of NH_4 resin took up about 2 mEq of Na. But in three patients who were receiving little Na a lesser amount of Na was taken up—about 0.7 mEq/g. without added K and only 0.2 mEq/g. when K was added to the diet. The amount of Na taken up per gramme of resin did not apparently depend on the dose of resin given.

It is possible that when only small amounts of Na are available, either because the intake is low or because the intestinal secretions contain less Na (Berger and Steele, 1952), the resin may be free to take up K and other ions in greater amounts. Though this does not apparently happen with carboxylic resins, our results suggest that with the sulphonated resin the uptake of other ions may be inversely related to the uptake of Na.

The resin can take up more K than is provided in the diet and can cause depletion of K. Unfortunately such depletion is not always revealed in good time by a fall in the serum level of K: with acidosis, in particular, the serum level may not fall and renal loss may persist in the face of a deficit. Depletion of K is undesirable: on a conservative view it produces apathy and anorexia; it can predispose to oedema; it may potentiate the effects of digitalis and produce myocardial lesions. An attempt is made to overcome the risk of depletion when the resin is given partly combined with K, as in katonium. Nevertheless if given with a diet low in Na this type of resin might combine with more K than it provides and it might remove significant amounts of Mg. It may prove necessary with some diets to add K and even Mg to the treatment, though an excess of cations given with the resin would render it less effective for combining with Na. Laboratory control will be necessary if the resin is to be used effectively and without danger of K depletion and acidosis.

Summary

In three balance experiments a cationic exchange resin (zeo-karb 225) was given in H or NH_4 form to two normal persons in a daily dose of 60 and 90 g. The diets contained about 200 mEq of Na, 31–38 mEq of K, and 12–22 mEq of Mg. With either form of resin and with both doses the resin took up Na, K, and Mg in a fairly constant ratio of about 11 : 5 : 1. Ca was not taken up. The amount of Na taken up by the NH_4 form was about 2 mEq/g.

In three patients with a low intake of Na the amount of Na taken up was only 0.7 mEq/g., and was further diminished when K was added to the treatment.

The capacity of the resin *in vivo* was estimated from the change in faecal excretion of cations and also, for the NH_4 form, from the change in faecal N. The capacity of the two forms of resin *in vivo* approached their capacity *in vitro*; that of the NH_4 form was about 3 mEq/g. *in vivo*.

With resin, the change in daily excretion of acid and ammonia in the urine was approximately the same as the change in excretion of cations in the faeces.

The results suggest methods of assessing the capacity of the resin *in vivo*. The capacity of the resin *in vivo* and the proportions of Na, K, Mg, and Ca that combine with the resin may well vary with the amounts of Na, K, Mg, and Ca in the intestine.

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REFERENCES

Berger, E. Y., and Steele, J. M. (1952). *J. clin. Invest.*, **31**, 451.
Fourman, P. (1952). *Lancet*, **1**, 1042.
—— and Ainley-Walker, K. M. S. (1952). Ibid., **2**, 368.
Greenman, L., Peters, J. H., Mateer, F. M., and Danowski, T. S. (1951). *J. clin. Invest.*, **30**, 1027.
Lancet, 1950, **2**, 367.
McChesney, E. W. (1952). *Amer. J. Physiol.*, **168**, 44.
—— Dock, W., and Tainter, M. L. (1951). *Medicine, Baltimore*, **30**, 183.
MacIntyre, I., and Jordan, A., (1951). *Lancet*, **1**, 965.
Sartorius, O. W., Roemmelt, J. C., and Pitts, R. F. (1949). *J. clin. Invest.*, **28**, 423.

A new British Standard for Fireguards and Heating Appliances (B.S. 1945:1953) has now been prepared. Its object is to assist the implementation of regulations which are to be issued by the Home Office under the Heating Appliances (Fireguards) Act. The new specification applies to all types of gas fires, electric fires, and oil-burning heaters used for domestic purposes. Guards must pass a test designed to control size of opening; a scorching test, in which a piece of flannelette is placed in contact with the guard and must not smoulder or ignite within a specified time; and a test for mechanical strength. Heating appliances provided with guards in accordance with this new specification are required to be marked with the words "Guarded in accordance with B.S. 1945." Copies of the standard may be obtained from the British Standards Institution, Sales Branch, 24, Victoria Street, London, S.W.1, price 2s.

THE EFFECT OF NIKETHAMIDE BY MOUTH IN MAN

BY

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Nikethamide was introduced as a therapeutic agent about twenty-seven years ago under the trade name of "coramine." It is also known as "anacardone," "corediol," "corvotone," "nicamide," and "nikethamol." This paper deals with the effects of the drug administered by mouth in man. The study has been prompted by the apparent difference of opinion which exists about its therapeutic value when given by this route.

Faust (1925) states that the drug is active when given by mouth, but does not make it clear if this refers to the human subject; Kohlhoff (1928) found that the convulsant dose in the rabbit by mouth was five times as great as the convulsant dose by intravenous injection. Dodds (1936) states that it exhibits a very powerful action in small doses by mouth in experimental animals. There are a number of references to the value of oral nikethamide in the treatment of cardiac dyspnoea, coronary artery disease, and peripheral circulatory failure, but the published details are inconclusive (Lankford, 1930; Daly, 1933; Winslow, 1936; Timmons, 1937; Lerner, 1937; Cowan, 1937, 1938; Stroud and Twaddle, 1940; Gayid, 1952; Morwood, 1952). The *British Pharmacopoeia* assigns it an oral dose of 0.25–1 g. or 1–4 ml. (as it is always used in a 25% solution), which is the same as the dose by parenteral injection, and it is employed especially in general practice in this dose, usually three times daily. The current editions of the standard textbooks on pharmacology and therapeutics, on the other hand, are not enthusiastic about its oral use, statements such as "of doubtful efficacy" or "not very powerful" being the rule. Modern textbooks on cardiology do not mention its use by mouth (Wood, 1950; White, 1951). It therefore seemed worth while to find out whether the actions of the drug, as seen after parenteral injection, could be reproduced in conscious subjects by oral administration.

Clinical Trial

Briefly the effects of 4 ml. given *intravenously* in the conscious subject are as follows. Pain is felt along the line of the vein, and within 10–15 seconds obvious hyperpnoea occurs, with usually but not always an increase in the rate of breathing. At the same time the patient experiences a feeling variously described as "hot and cold," "funny feelings," "pins and needles," throughout the body and especially in the face, fingers, and toes. The blood pressure and pulse rate rise to a variable degree, and sweating about the hands and face occurs; the whole effect is remarkable for its short duration, being completely over in a few minutes. In apprehensive subjects greater changes in the pulse rate, blood pressure, and respiratory rate are seen than in those who are less nervous, but the hyperpnoea and subjective paraesthesiae are invariable. It was thought that these effects might be reproduced by oral administration. A dose of 5 ml. five times daily was given to eight different subjects on ten different occasions for periods varying from 3 to 26 days, and records of the pulse rate, respiration, and blood pressure were taken frequently. In addition urinary output and electrocardiograms were recorded in some cases. All these patients had been observed in hospital for a prolonged period. All suffered from chronic heart failure with dyspnoea, and oedema was present in four cases. In four subjects nausea occurred and some doses were vomited, but otherwise the results were negative.

An attempt was then made to obtain some obvious effect by increasing the dose to 10 ml. five times daily. This dose was given to four different subjects, but in all of them it had to be abandoned after three to four days because of nausea and vomiting. Significant changes in the pulse and blood pressure did not occur and changes in breathing were not seen apart from those associated with nausea and the act of vomiting.

Single doses of 16 ml. were given to six subjects: four had chronic heart failure, one suffered from bronchial asthma, and one was a healthy subject. Nausea was experienced by all six patients and vomiting occurred in two, but again no effects such as are seen after intravenous injection were noted.

Finally, doses of 30 ml. were given to three subjects, all suffering from chronic heart failure. In one the dose was promptly vomited. In the other two it was retained with encouragement, though considerable nausea was produced, but no significant changes were seen in the depth and rate of breathing nor in the pulse and blood pressure.

Comment

In all, nikethamide has been given in these large doses to 20 different subjects without any indication of effect apart from nausea and vomiting. It would seem that the characteristic action of the drug is hard to obtain by oral administration, and it is very doubtful indeed if in the doses in which it is commonly given (1–2 ml. three times daily) it can have any pharmacological action of therapeutic value. Indeed, these small doses barely produce any effect even when given intravenously.

It is realized that the simple methods of bedside observation which have been employed may not have been sensitive enough to record minimal changes, but the therapeutic value of the drug is best ascertained by these clinical techniques. An attempt is now being made to evaluate the drug on the basis of blood levels of free nikethamide attainable by the various routes of administration. Probably the main value of this biochemical development will be to throw further light on the metabolism of nikethamide, which in turn may account for the failure of the drug to produce its characteristic action when given by mouth to the human subject.

Summary

Nikethamide was administered orally in doses of 5 ml. and 10 ml. five times daily, and in single doses of 16 ml. and 30 ml. It produced no effects on the cardiovascular or respiratory system. When symptoms and signs of cardiac failure were present they were not affected by the treatment.

My thanks are due to Professor Stanley Alstead for encouragement and help in the preparation of this paper.

REFERENCES

Cowan, J. H. (1937). *Amer. J. med. Sci.*, **193**, 673.
—— (1938). *J. Lab. clin. Med.*, **24**, 225.
Daly, A. A. (1933). *Med. J. Rec.*, **137**, 467.
Dodds, E. C. (1936). *Proc. roy. Soc. Med.*, **29**, 655.
Faust, E. S. (1925). *Lancet*, **1**, 1336.
Gayid, I. K. (1952). *Ibid.*, **1**, 1165.
Kohlhoff, H. (1928). *Arch. exp. Path. Pharmak.*, **136**, 331.
Lankford, J. S. (1930). *Clin. Med. Surg.*, **37**, 670.
Lerner, H. (1937). *Med. Rec.*, **145**, 49.
Morwood, J. M. B. (1952). *Practitioner*, **168**, 67.
Stroud, W. D., and Twaddle, P. H. (1940). *Ann. intern. Med.*, **14**, 361.
Timmons, E. R. (1937). *Med. Rec.*, **146**, 227.
White, P. D. (1951). *Heart Disease*, 4th ed., New York
Winslow, K. (1936). *Northw. Med., Seattle*, **35**, 369.
Wood, P. (1950). *Diseases of the Heart and Circulation*. London.

Medical Memorandum

Jejunal Diverticulitis with Diverticular Concretion

In an exhaustive review of the complications of acquired diverticulosis of the jejunum and ileum, Milnes Walker (1945) pointed out that in no case of jejunal diverticulitis had a concretion ever been found in an inflamed diverticulum, a fact suggesting that such concretions do not predispose to inflammation. I have found only one case of concretion formation reported since 1945, and this occurred in an uninflamed diverticulum. It was reported by Klidjian (1946).

The case recorded below therefore seems unique in that a concretion was found in a jejunal diverticulum which was the site of acute diverticulitis. It is also of interest because simple local excision of the diverticulum was practicable, which is unusual in cases of jejunal diverticulosis.

CASE REPORT

A housewife aged 60 was admitted to hospital on July 18, 1949, complaining of nausea and abdominal pain. The pain had started thirty hours previously as periumbilical colic, and had been continuously present since, increasing in intensity until it became "as bad as labour pains." It was accompanied by a feeling of abdominal distension, right-sided soreness, and a little lumbar backache. No previous history of any abdominal upset could be obtained.

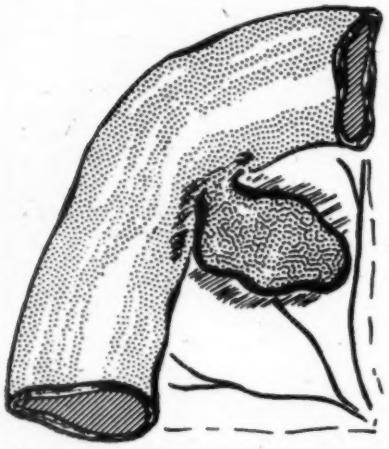

Diagram illustrating the operative appearance. The inflamed diverticulum, with contained concretion *in situ*.

Examination showed great tenderness of peritoneal type above and to the right of the umbilicus, and also high right-sided tenderness on rectal examination. Bowel sounds were present. The temperature was 100.2° F. (37.9° C.). The tongue was heavily coated. Although a provisional diagnosis of acute appendicitis was made mental note was taken that the clinical picture did not seem entirely typical of that condition.

Operation.—A right lower paramedian incision was made under general anaesthesia. Some free fluid was present, and some distance below the duodeno-jejunal flexure there was a hard movable rounded mass, about the size of a golf ball, attached to the mesenteric aspect of the small gut. When withdrawn from the incision the mass proved to be an inflamed solitary diverticulum of the jejunum containing a concretion or enterolith 1 in. (2.5 cm.) in diameter. The diagram shows how this diverticulum presented on the left-hand aspect of the mesentery at a point on the jejunum 2 ft. (61 cm.) below the duodeno-jejunal flexure. In spite of the inflammatory oedema in the related part of the mesentery and nearby jejunal wall, and because of the narrow neck, diverticulectomy and jejunal repair, using two layers of catgut sutures and an omental graft, were easily accomplished without any narrowing of the jejunal lumen. The appendix was removed too, but it looked entirely normal. No other abnormality could be found in the abdomen, and in particular there were no other diverticula.

Convalescence was uneventful, and the patient was discharged home with the wound healed on the ninth post-operative day. She was seen and re-examined six months after the operation, when she reported fit and well, and said that she had been able to dispense with the laxatives she had previously found necessary.

COMMENT

The diverticulum had only a very thin and tenuous muscle coat, and seemed a typical acquired (rather than a congenital or cyst-like) diverticulum, which lay in close relationship to the left branch of one of the vasa recta. The contained concretion completely filled the lumen. Fusiform in shape, it was about 1 in. (2.5 cm.) long, of hard consistence, and brownish yellow in colour. By a misfortune it was lost on the way to the laboratory and so never came to analysis, but I believe that it probably was a bile-acid enterolith of the type described by Armitage, Fowweather, and Johnstone (1950).

Diverticula of the small intestine are comparative rarities, and those containing concretions are very rare indeed. Orr and Russell (1951) reported a series of 13 cases of jejunal diverticulosis, but they do not record concretion formation in any; nor did Edwards (1939), in his classical series of 16 cases. In addition, in the series of 122 cases of jejunal and ileal diverticulosis reported from the Mayo Clinic, Benson, Dixon, and Waugh (1943) do not mention concretion formation. Milnes Walker (1945) was able to find only four previously recorded cases of concretion formation in jejunal diverticula. In three of these the concretions had caused acute intestinal obstruction. He reported a case in which an inflamed ileal diverticulum had been found to contain a concretion, and noted that several other authors had reported cases of concretion formation in duodenal diverticula. Soon afterwards Klidjian (1946) reported his case, in which severe melaena had been caused by haemorrhage from a jejunal diverticulum containing a large concretion of unspecified type.

It would therefore seem that the present case of jejunal diverticular concretion is only the sixth reported, and in fact it is the only one in which a concretion has been found in an inflamed jejunal diverticulum.

It is a pleasure to thank Mr. D. M. Sutherland, under whose care this case was admitted, for much help and encouragement, and I am indebted to Dr. Robert Ollerenshaw, and Mr. Kilshaw, of the department of medical photography at the Manchester Royal Infirmary, for the illustration.

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REFERENCES

Armitage, G., Fowweather, F. S., and Johnstone, A. S. (1950). *Brit. J. Surg.*, **38**, 21.
Benson, R. E., Dixon, C. F., and Waugh, J. M. (1943). *Ann. Surg.*, **118**, 377.
Edwards, H. C. (1939). *Diverticula and Diverticulitis of the Intestine.* Wright, Bristol.
Klidjian, A. (1946). *British Medical Journal*, **1**, 683.
Orr, I. M., and Russell, J. Y. W. (1951). *Brit. J. Surg.*, **39**, 139.
Walker, R. M. (1945). *Ibid.*, **32**, 457.

A new quarantine station will be put into service at Jeddah, the port of Mecca, for the pilgrimage season of 1953 (Year of the Hegira, 1372). The Government of Saudi Arabia is completing its construction and the World Health Organization is helping to equip and staff it. It will replace the old station of Kamaran, situated on an island in the southern part of the Red Sea, where, between the two world wars, up to 100,000 pilgrims were handled during one year (1926–7). The station at Jeddah comprises a quarantine station for the accommodation of persons under observation, a communicable diseases hospital, a general hospital, and a laboratory. On several occasions in the past the pilgrimage to the holy places in the Hedjaz has been the cause of serious epidemics, notably of plague and cholera. At its own request, the Government of Saudi Arabia is responsible for the new station under the International Sanitary Regulations.

Reviews

ABDOMINAL SURGERY

The Management of Abdominal Operations. Edited by Rodney Maingot, F.R.C.S. (Pp. 1,256; 532 illustrations in 328 figures. £6.) London: H. K. Lewis and Co. 1953.

The appearance of this remarkable volume forms an epoch in the history of modern surgery. It records the experiences and the achievements of 33 of the acknowledged leaders in British surgery, set out with lucidity, brevity, and candour. Much that is to-day accomplished with almost routine facility would 20 years or even 10 years ago have been utterly impossible, and it is doubtful if any other art can show such solid and continuous progress.

It is remarkable that just one-third of the book is devoted to considerations which are essentially physiological—a striking contrast to the atmosphere of anatomy in which we surgeons were trained in another epoch. To-day the surgeon must have this knowledge, but the human brain does not expand, and one wonders how long he can carry such a burden and whether we must not in the future achieve some division of responsibility.

The contents of the book are so good and so varied that no review could possibly do them justice. We can only mention the really fine articles by Maingot on the stomach and on the biliary tract, by Norman Tanner on gastric haemorrhage and perforation, and by Borrie on the oesophagus and the cardia. But standing above everything else is the great essay by Gordon-Taylor on abdominal injuries in warfare and in civil life, an essay which really makes history and which only its author could have written.

HENRY SOUTTAR.

HANDBOOK OF OBSTETRICS

A Modern Practice of Obstetrics. By D. M. Stern, M.B., B.Ch.(Cantab.), F.R.C.S., F.R.C.O.G., and C. W. F. Burnett, M.D.(Lond.), F.R.C.S., F.R.C.O.G. Line drawings by Susan M. Robinson. (Pp. 248; 140 illustrations. £1 15s.) London: Baillière, Tindall and Cox. 1952.

This book, intended for medical students, is based on the writers' experiences at the West Middlesex Hospital. It is rather smaller in size than the average undergraduate textbook but is in no way a "synopsis." In order to keep it concise, pure anatomy and physiology have been entirely omitted, while, according to the preface, normal and common abnormal conditions have been emphasized and the rarer complications but briefly mentioned.

The authors have aimed "to write upon the subject from a new aspect" and avoid the repetition of unsubstantiated statements which sometimes "have found their way from the pages of one textbook to those of another." In this they have largely succeeded, although it may be thought that a few clinical myths have in fact been perpetuated, such as the alleged predisposition of the elderly primigravida to uterine inertia. Again, on some controversial topics the authors' opinions, dogmatically expressed, will not meet with general acceptance. For example, their preference for face-to-pubes delivery with Kielland's forceps in persistent occipito-posterior cases, their view that uterine inertia commonly recurs, their approval of a laterally placed episiotomy, and their condemnation of all mucus extractors are all matters which will provoke criticism.

Because of the omission of the basic sciences the uninitiated student may sometimes be bewildered when confronted with a new term (for example, "diagonal conjugate") without explanation—even though there is an appended glossary of terms. Despite the promise contained in the preface, the balance between common and uncommon conditions is not always well preserved. Most of the normal and important abnormal conditions are adequately described, yet ante-partum haemorrhage—surely an important subject—receives only a brief description and is altogether oversimplified. On the other hand, space is given to the mention of some rare conditions such as the Chiari–Frommel syndrome.

The book is well written and "readable." It is produced in an unusual format—larger in page size than is the custom and printed in double column—and is a refreshing breakaway from the traditional students' handbook. There are numerous line drawings, most of which are clear and explanatory. Each chapter is headed by an apt Shakespearean quotation and clearly divided by subheadings. Pleasing features are the inclusion of an appendix on "Obstetrical Terms Defined" and another (3½ pages of double column) on "Etymology." There are few printers' errors, although page 156 contains a mistake, and on page 189 two diagrams are incorrectly labelled.

Such criticisms as are advanced are not intended to detract from the considerable merits of this book. It is a welcome production and can be recommended to readers wanting a short textbook that is "different."

MOSTYN P. EMBREY.

LOCAL ANALGESIA

Local Analgesia: Abdominal Surgery. By R. R. Macintosh, D.M., F.R.C.S.Ed., D.A., and R. Bryce-Smith, B.M., B.Ch., D.A. Illustrated by Miss M. McLarty. (Pp. 94; 88 figures. £1 2s. 6d.) Edinburgh and London: E. and S. Livingstone. 1953.

The introduction of curare and other specific relaxants of muscle has tended to obscure methods of local analgesia in abdominal surgery, for a single intravenous injection is easy to give and is more rapid in its effects than infiltration and multiple nerve blocks. Nevertheless, as the authors of this excellent monograph point out, local analgesia still has its place, not only for abdominal surgery but in the diagnosis and treatment of many diseases. The recent introduction of lignocaine ("xylocaine") has stimulated interest in local techniques, since this drug has a rapidity of onset and reliability greater than other agents in concentrations of equal toxicity.

The various methods are described in sufficient detail for practical use, and the vagueness so annoying in many books of this nature is avoided. The illustrations are prolific, well drawn, and often in colour—features now associated with publications from the Nuffield Department of Anaesthetics. No mention could be found of the use of hyaluronidase as an aid to the successful blocking of deep nerves, which the reviewer has found valuable (though the authors can justly retaliate by saying that his knowledge of anatomy is not up to the Oxford standard). The printing, paper, and binding are first class, but the price is distressingly high.

C. LANGTON HEWER.

HAZARDS OF ATOMIC ENERGY

Biological Hazards of Atomic Energy. Edited by A. Haddow. Being the papers read at the Conference convened by the Institute of Biology and the Atomic Scientists' Association, October, 1950. (Pp. 235. £1 15s.) Oxford: The Clarendon Press. 1952.

Between these covers will be found a series of papers delivered by experts to their peers. Fortunately for the general reader the experts were of many branches, so that usually the content is not so abstruse as to be really difficult: the wind was tempered for other lambs of the same flock. As for the medical reader, it may be hoped that he will be effectively impressed with the possible dangers of atomic energy, but also with the possibility of escaping them by adopting a technique or ritual no more complicated than that used in aseptic surgery. Pochin's article on the clinical use of radio-iodine is an excellent description of such a technique. Another useful piece of evidence is Marley's report on 51,077 weekly monitoring films at Harwell; only 77 exceeded 0.2 r, and none at all were over 3 r. Clearly, then, safety can be and should be attained, but equally

clearly no one should expose himself or others to any risks at all unless he has learnt in a proper school how to avoid them.

Loutit's article on possibilities of protection against massive doses of ionizing radiation holds out hope that something more than shielding may be attainable when the fundamental action on tissues is better understood. Neary's contribution, which clearly indicates the nature of the hazards associated with the dangerous tools now put into doctors' hands, should certainly be studied. The geneticists have their say, and arrive at results which bear a gloomy aspect; nevertheless, the warning they give should be noted. As Mather says, "It is our plain duty to avoid all unnecessary and unjustifiable radiation of the germ line."

For all those engaged in work with radiation sources this book is one that should always be within reach and constantly consulted.

E. ROCK CARLING.

SEWAGE DISPOSAL

Small Sewage Disposal System (with special reference to the Tropics). By O. J. S. Macdonald, M.D. (Pp. 300; 92 illustrations. 20s.) London: H. K. Lewis and Co. 1952.

As the author of this book points out, there was previously no single volume recording the range of small sewage-disposal systems suitable for rural areas. He therefore describes the methods which he has proved to be satisfactory under ordinary conditions of use in the Tropics. He includes an account of almost every type of latrine or sewage-disposal installation which may be set up in sewerless areas for the individual house or for small communities numbering up to 200 persons, and discusses its advantages and disadvantages.

In the first part of the book the author considers problems of construction and practice. After three general introductory chapters he writes on domestic and communal water-borne systems using septic tanks, the purification and disposal of the effluent, the pour-flush latrine and aqua privy, pit and bucket latrines, and the maintenance of disposal systems. The second part of the book is on the nature of sewage, its biological treatment, and the principles involved in the design and functioning of septic tanks. There are two chapters listing, with descriptions, the many different designs of septic tank and aqua privy which have been adopted by sanitary authorities and experts in various parts of the world.

This is an extremely practical volume which may be strongly recommended to medical officers, sanitary engineers, and sanitary inspectors working in rural areas, particularly of the Tropics. The descriptions are lucid, and are accompanied by nearly 300 drawings in which dimensions and constructional details are given. Bills of quantities prepared by an engineer are provided in the case of the more popular systems, and costs in Ceylon are recorded. In fact, the author has included almost every item of information which anyone may require on the choice, construction, or maintenance of a small sewage-disposal installation.

T. H. DAVEY.

SOCIAL PSYCHIATRY

Social Psychiatry. By Maxwell Jones, M.D., M.R.C.P.(Ed.), D.P.M., *et al.* (Pp. 186. 18s.) London: Tavistock Publications, Ltd. 1952.

Dr. Maxwell Jones and his six collaborators describe the development and realization of an idea—from its first beginnings in a unit for the treatment of effort syndrome during the war, and later in a unit for the rehabilitation of returned prisoners at the end of the war, to the present Industrial Neurosis Unit at Belmont Hospital. The purpose of this unit, as its name implies, is the treatment of neurotic patients who are partly or completely disabled. In fact, many of them have been unable to work for years, and some have few prospects of returning to work under any but sheltered conditions.

The idea which inspired Dr. Jones, and through him his staff, was that of creating a society in which these social misfits might enter and actively participate. The central problem was morale; merely submissive co-operation on the part of the patient was not enough, and he had to be induced to enter into the spirit of the community life provided for him. This has been the rationale behind the various techniques which have been developed—for example, group discussions to which patients contribute both in providing their own problems and in advising on those of others, and "psychodrama," in which the same themes, in playlets written and acted by patients, receive a more dramatic and stimulating form.

It seems needless to add that there are many other aspects to the work done at this centre at Belmont—investigation along normal psychiatric lines, the testing of intelligence and assessment of employability, a work programme with workshops and physical training, the social study of the patient's private world, and liaison with the rehabilitation officers of the Ministry of Labour. The final aim is to get the patient back into satisfactory working life, and a happier life personally. In view of the fact that the treatment of chronic neurosis is exceedingly difficult and discouraging, a figure of 44% of patients making sound adjustments after discharge must be regarded as very satisfactory.

ELIOT SLATER.

CARDIOVASCULAR DISEASES

Clinical Progress in Cardiovascular Disease. Edited by Herrman L. Blumgart, M.D. Modern Medical Monographs. (Pp. 143. $4.50.) New York: Grune and Stratton. 1952.

In December, 1950, the American journal *Circulation* started a new monthly feature: "Clinical Progress." These critical reviews of important subjects have been well received, and several of them are now presented together in book form. The subjects chosen include atherosclerosis, the management of acute cardiac emergencies, surgery for mitral stenosis, the management of cardiac patients in relation to surgery, and emotion and the circulation.

The chapter on atherosclerosis, to which Louis Katz, Ancel Keys, and John Gofman contribute, will be widely acclaimed. The relationship of certain classes of serum lipoprotein (Sf 12–100) to atherogenesis can no longer be disputed, and it is clear that the serum cholesterol has only indirect bearing on the disease, depending on its relationship to the lipoprotein classes mentioned. Each of the contributors presents independent evidence that a diet low in total fat influences atherogenic activity favourably, the nature of the fat, whether animal, vegetable, or cholesterol-bearing, being unimportant. But much more than this is discussed—for example, the part played by hypertension, sex, vascular injury, and lipotrophic substances. There is little doubt that a vast amount of work on this grave disease is gradually bearing fruit, and it may not be long before atherosclerosis can be in some measure controlled.

The account of the management of acute cardiac emergencies by de la Chapelle and Rose is didactic and practical. The advice is orthodox except in recommending intravenous digoxin in preference to aminophylline in cases of acute left ventricular failure. The surgical treatment of mitral stenosis is discussed by E. F. Bland. He traces the history of this great surgical achievement admirably, but surveys the present situation less well. The management of cardiac patients in relation to surgery is described by A. C. Ernstene, the effect of emotion on the circulation by Mark Altschule. Both these chapters are sound so far as they go.

Just what finally decided the editor to choose these five contributions out of the 20 reviews so far published in *Circulation* is not clear. The reasons given are pertinence to significant problems of current interest and practical usefulness. Personally I should be content, and honoured, with a reprint of the article on atherosclerosis.

PAUL WOOD.

BRITISH MEDICAL JOURNAL
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STREPTOMYCIN AND ISONIAZID

The series of clinical trials organized by the Medical Research Council to test chemotherapeutic agents in tuberculosis has been notable not only for the results achieved but also for the advance in technique which has enabled questions to be answered in a matter of months that with former methods would have taken years. By analysing the results as the trial progressed it was possible to publish[1] the first report on the use of isoniazid in pulmonary tuberculosis only six months after starting the trial and a second important report, published this week in our opening pages, only five months later. Great credit is due to the many clinicians and bacteriologists who have worked almost anonymously and who have contributed so much. With such widespread team-work it is almost invidious to mention names, but a special tribute must be accorded to Dr. Marc Daniels, the chief co-ordinator of all these trials since their inception. His death earlier this week is a grievous loss to the Medical Research Council and to British medicine.

The present report gives the results of three months' treatment of 364 patients suffering from pulmonary tuberculosis of different degrees of severity. Of these, 142 were treated with streptomycin 1 g. daily and isoniazid 100 mg. twice a day, 102 with streptomycin 1 g. daily and sodium *para*-aminosalicylate (P.A.S.) 20 g. daily, and 120 with isoniazid 100 mg. twice a day alone. Over this period streptomycin and isoniazid, given together, were superior to streptomycin and P.A.S. in their effect on weight gain and blood sedimentation rate, and rather more effective in improving general condition. There was no significant difference in the effect on pyrexia, sputum-conversion, or the radiographic appearances. Comparison of streptomycin and isoniazid with isoniazid alone, over the same period, showed that the combined treatment was much more effective in lowering the sedimentation rate and improving the radiograph. It was slightly more effective in returning the temperature to normal. The effect on general condition and on weight was similar with both treatments.

The tests for sensitivity of the tubercle bacilli to the drugs are as important as the results of the different treatments. Positive cultures from patients treated with isoniazid alone showed drug-resistant tubercle bacilli in 11% of the cultures after one month's treatment, in 52% after two months', and in 62% after three months'. When streptomycin was added, isoniazid-resistant bacilli were obtained in only 4% of positive cultures at one month, 9% at two months, and 13% at three months. The difference is even more impressive when negative cultures are taken into account. After three months' treatment isoniazid-resistant bacilli were obtained from 35% of patients treated on isoniazid alone, compared with only 3% of patients treated with streptomycin and isoniazid. Naturally it is not known what percentage of patients with negative cultures may be harbouring undetected resistant bacilli. When a comparison was made of the emergence of streptomycin-resistant organisms in the two groups on combined treatment, no great difference was found after one or two months' treatment. Expressed as a proportion of positive cultures, 2% were resistant at one month with streptomycin and P.A.S., compared with 1% for streptomycin and isoniazid; at two months the figures were 3% and 4% respectively. At three months 24% of positive cultures were resistant to streptomycin in the group treated with streptomycin and P.A.S., compared with 11% of cultures in the group treated with streptomycin and isoniazid. Expressed as a percentage of patients treated, this looks less formidable: resistant organisms were isolated from 5% of those treated with streptomycin and P.A.S. compared with 2% of those on streptomycin and isoniazid. The percentage resistant in the streptomycin–P.A.S. group is unduly high. When allowance is made for cultures P.A.S.-resistant before the start of treatment, the figures for streptomycin resistance fall to about 13% of cultures and 2.5% of patients, which are comparable to the results for the streptomycin–isoniazid group.

It is clear from this and the previous Medical Research Council report that isoniazid should no more be used alone than should streptomycin or P.A.S. When any of these drugs is given alone, resistant tubercle bacilli are likely to emerge. Moreover, if in the same patient the relevant drug is later used in combination, it will be found to have lost its capacity to prevent or delay resistance to the other member of the combination. On the other hand, isoniazid 200 mg. daily given with streptomycin 1 g. daily seems to be the most effective combination so far available, even though its proved superiority over streptomycin and P.A.S. is seen only in weight gain and blood sedimentation rate. Isoniazid has the additional advantage over P.A.S. of negligible toxicity in the doses used. When streptomycin and isoniazid are given together, the reciprocal suppression of drug

[1] *British Medical Journal*, 1952, **2**, 735.

resistance is of the same order as that of streptomycin and P.A.S. over a three-month period. But the few available figures for isoniazid resistance at four months are less reassuring. Three out of eight positive cultures were resistant, though in most of these patients streptomycin was given only three times a week in the fourth month. Until more evidence is available these results suggest caution in giving streptomycin less often than once daily when it is used with isoniazid, and we do not know that the combination will maintain its clinical superiority when continued for more than three months. The patient being treated with streptomycin and isoniazid is having the advantage of the two most powerful drugs at present available, but if tubercle bacilli emerge which are resistant to one they will probably become resistant to the other; in short, all one's chemotherapeutic eggs are in one basket. In view of this it would seem rational to confine streptomycin and isoniazid to certain types of case. When chemotherapy will probably be the definitive treatment of a patient—for instance, with relatively localized recent disease without cavitation—resistant organisms are less likely to emerge and it is reasonable to risk using the best combination. It is also justifiable if the patient is quite intolerant to P.A.S. or if, because of previous treatment with P.A.S. alone, there is strong possibility that the organisms are P.A.S.-resistant. In patients with cavities or with more extensive disease it is wiser to start with the well-tried streptomycin and P.A.S., keeping isoniazid in reserve in case the bacilli become resistant. Occasionally the patient's bacilli may be resistant to streptomycin but not to P.A.S.; combination of isoniazid with P.A.S. is then appropriate, though we have as yet no evidence on its efficacy. When patients are desperately ill, it is reasonable to give them all three drugs in the first place, but again it may be advisable to withdraw isoniazid into reserve as soon as the most acute phase has been controlled. If, because of resistance to streptomycin and P.A.S., the patient has to receive isoniazid—which has been kept in reserve—its use should be carefully timed to cover a crisis. The last important chemotherapeutic reserve must not be frittered away.

It must be remembered that patients may have been primarily infected with resistant bacilli. The bacilli of four patients in this series were initially resistant to streptomycin, though they had had no previous chemotherapy. Resistance tests on pre-treatment cultures are therefore essential. It may be impossible to defer treatment until results become available, but, as suggested in the report, one should take note of the chemotherapy given to known contacts before deciding on the best combination for the patient. Clearly therefore every case must be carefully assessed before deciding on the appropriate form of chemotherapy. The possibility of drug resistance should always be borne in mind, and adequate information on drug sensitivity should be available at important stages in the patient's treatment. A culture at the end of the course of chemotherapy (or the last positive culture) should always be tested for drug-sensitivity.

The chemotherapy of tuberculosis is no longer simple. Its very success and diversity are creating ever-changing problems with which everyone who treats the disease must become familiar. The pace of research is such that even the conclusions of the present authoritative report may be out of date in a few months.

EPIDEMIC NAUSEA AND VOMITING

During the past few years many general practitioners and some medical officers of health[1–4] have been encountering an epidemic infection which, because it is mild and apt to be misdiagnosed, has not attracted much official attention. It is a disease characterized by nausea and vomiting of sudden onset, some initial fever and general aching, and in some cases giddiness, anorexia, and diarrhoea. The syndrome has a variety of synonyms such as epidemic viral gastro-enteritis, winter vomiting disease (because outbreaks occur more often in the winter), epidemic diarrhoea and vomiting, and gastric flu. This last diagnostic title, while apt, is likely to cause confusion if the outbreak of epidemic vomiting coincides with an epidemic of influenza, as has happened this winter. A false clinical picture of the syndrome may thus be obtained, in that respiratory symptoms may appear to be an integral part of the disease. But in school outbreaks, such as those recently reported by Garland[2] and by Dummer,[4] respiratory symptoms have been notably absent.

This is no new disease. School outbreaks of a similar nature were reported by Miller and Raven[5] in 1936, by Gray[6] in 1939, and by Bradley[7] in 1943, while some years ago epidemic diarrhoea and vomiting was a prevalent infection in maternity units, affecting both mothers and infants.[8] However, profuse watery diarrhoea with or without vomiting was the principal symptom in these maternity hospital outbreaks, and it may be that there are two separate clinical entities.

When outbreaks occur in schools some form of food-poisoning is often suspected, but investigation shows that the outbreak has not the explosive character of a food-borne infection and has no close

correlation with the distribution of water, milk, or other foods, while bacteriological examination of stools, vomit, or suspected foods is invariably negative. Certain clinical features also help to distinguish epidemic vomiting from food-poisoning. Thus the sudden unexpected onset of projectile vomiting, most often in the middle of the night, has been an outstanding feature; giddiness has been a fairly common accompaniment, and there is often some general aching, with a frontal headache which tends to come and go. Fever up to 100° F. (37.8° C.) occurs at the onset. Abdominal signs are usually limited to some epigastric discomfort, and there are no colicky pains. The illness usually lasts for one to three days, but relapses may occur about one week after recovery. The nature of the clinical symptoms has suggested some disturbance of the central nervous system, but no direct evidence of its involvement has been described.

The disease is highly infectious, and the attack rate in a susceptible community varies from 10% to over 80% according to intimacy of contact. Outbreaks seem to occur most often in the autumn or winter, but no season is exempt. The incubation period may vary from two to seven days but is usually short, so that the infection spreads quickly through a school community. The epidemiological evidence suggests that the infection is spread by the respiratory route, although indirect spread by contaminated articles or food certainly cannot be excluded. The causative agent is unknown but is believed to be a virus. Gordon and his colleagues[9] were able to infect human volunteers by feeding them with faecal filtrates or unfiltered throat washings from infected cases, whereas no symptoms occurred after inhalation of the throat washings. Attempts to infect the chick embryo and various experimental animals have been unsuccessful.

Although infectious syndromes of unusual nature may attract attention when they occur in schools or other institutions, clearly if they are of short duration and relatively mild they may be prevalent in the general community yet entirely escape official recognition by the health authority unless the general practitioner of his own accord notifies such cases to the medical officer of health. For example, it is clear from information received through the Public Health Laboratory Service that outbreaks of epidemic vomiting have been occurring among schoolchildren and students in many parts of the country during the past two or three years, yet no records of the prevalence of this infection are generally available. Much useful information about the clinical features and epidemiology of prevalent but non-notifiable illnesses might be collected if there were some arrangement for doctors in different areas to act as "spotters" of new maladies. Is this another job for the College of General Practitioners?

1 Silverton, M. I., *Med. Offr*, 1952, **88**, 215.
2 Garland, A., ibid., 1952, **88**, 241.
3 Berry, R. B., ibid., 1952, **88**, 262.
4 Dummer, F. H. M., ibid., 1953, **89**, 65.
5 *British Medical Journal*, 1936, **1**, 1242.
6 Ibid., 1939, **1**, 209.
7 Ibid., 1943, **1**, 309.
8 Brown, G., *et al.*, ibid., 1945, **2**, 524.
9 *J. exp. Med.*, 1947, **86**, 409.

AGRANULOCYTOSIS

Therapy of some kind is the usual cause of agranulocytosis. It was first described as a clinical entity in 1922, when Schultz[1] reported on six patients presenting with severe sore throat, prostration, and extreme reduction or disappearance of granulocytes from the peripheral blood. The number of reported cases increased steadily during the ensuing decade, largely owing to the use of amidopyrine in analgesic and antipyretic tablets. A few cases were caused by benzene, gold, and organic arsenicals. In 1933 the sale of amidopyrine was made illegal except on the prescription of a registered medical practitioner, and the frequency of cases due to this drug diminished. They did not completely disappear, because physicians continued to prescribe proprietary preparations without realizing that they contained amidopyrine.[2] During the last decade these older compounds have given way to newer ones as causes of agranulocytosis, and severe or total depression of granulocytes has been attributed to treatment with sulphonamides, thiouracil, tridione, P.A.S., chloramphenicol, isoniazid, and, most recently, "butazolidin."[3] While a therapeutic agent is the commonest cause of agranulocytosis, hairdressing chemicals may not be without blame: Cotter[4] has reported three cases caused by thioglycolic acid, a substance used in a "home cold-wave" process.

The mechanism by which chemicals cause agranulocytosis remains unknown. Possibly they derange the metabolism of the granulopoietic marrow cells. Often the condition develops suddenly and after only a small dose. This, together with the observation that urticaria, angioneurotic oedema, asthma, and other allergic manifestations may be associated, has led to the belief that some patients have an idiosyncrasy to the drug.

Prevention of agranulocytosis lies in avoiding drugs known to cause the condition, and, when this is impossible, in warning the patients to stop taking the drug and to report immediately if they develop malaise, a sore throat, or any other new symptom. It is doubtful if white cell counts at weekly or longer intervals are of use, for a normal white cell count on one day may be followed two days later by a precipitous fall in granulocytes.

The many treatments recommended bear testimony to the difficulty of obtaining enough cases to test the value of any one therapeutic agent. Indeed, the disease is so

1 *Dtsch. med. Wschr.*, 1922, **48**, 1495.
2 Discombe, G., *British Medical Journal*, 1952, **1**, 1270.
3 Ibid., 1952, **2**, 1401.
4 *J. Amer. med. Ass.*, 1946, **131**, 392.
5 Nelson, D. H., Sandberg, A. A., Palmer, J. G., and Tyler, F. H., *J. clin. Invest.*, 1952, **31**, 843.
6 Caldwell, A. L., *et al.*, *Canad. med. Ass. J.*, 1950, **62**, 506.
7 McMillin, J. S., *Amer. J. med. Sci.*, 1951, **222**, 392.
8 *Arch. Intern. Med.*, 1952, **90**, 580.
9 *British Medical Journal*, 1952, **1**, 1273.

dangerous that usually blunderbuss therapy is given. All workers are agreed that the offending drug must be withheld. The most beneficial single therapeutic measure is to give penicillin as soon as the condition is diagnosed; it must be continued until the granulocytes reappear in the peripheral blood. Marrow function usually returns within seven days, and, if the patient can be protected from infection while the leucocyte defences are down, spontaneous recovery is likely. Attempts have been made to increase the number of circulating granulocytes, and for this pentnucleotide, folic acid, pyridoxine, and liver extract have been recommended, but their value has still to be proved. Fresh blood transfusions have been used, but it is doubtful whether they provide viable leucocytes for a sufficient length of time to be of help to the patient.

Recently cortisone and adrenocorticotrophin (A.C.T.H.) have been tried, partly because they are known to influence allergic reactions and partly because they cause a leucocytosis in normal subjects. In fact the well-known eosinopenia caused by these agents is not so marked as the less well known increase in neutrophilic cells.[6] The course of agranulocytosis is so variable that it is difficult to assess the therapeutic value of A.C.T.H. and cortisone, and in the reported cases penicillin and other treatment were wisely given in addition. Two cases ascribed to sulphonamides recovered, but one of them showed improvement with early neutrophilic regeneration after treatment with penicillin and pentnucleotide and before the cortisone was given.[6,7] Virkkunen[8] reports two patients with rheumatoid arthritis who developed agranulocytosis following treatment with thiosemicarbazone: one had shown no improvement after six days of penicillin and the other after two days. Both appeared to respond promptly to A.C.T.H. Hart and his colleagues[9] have reported a case due to "novalgin"—a proprietary preparation containing a substance allied to amidopyrine—which still showed depression of myeloid marrow cells 13 days after treatment with penicillin, blood transfusions, and pyridoxine. There was a notable response to A.C.T.H. Although the findings in these cases are suggestive, there is no proof that cortisone or A.C.T.H. was really responsible for the improvement, which may have been spontaneous. Further trials, if possible properly controlled, are required. One note of warning must be sounded. Cortisone and A.C.T.H. increase the liability to infection, and if they are given to patients with agranulocytosis large doses of penicillin are more necessary than ever.

CHLOROPHYLL

We recently discussed the evidence for the statements which continue to be so widely circulated that chlorophyll preparations have a deodorant action.[1] In an effort to credit some of the less unlikely claims, such as that chlorophyll dressings reduce foul odours from wounds, too favourable an opinion may have been expressed. Many of us are inclined to think in a matter of this kind that there must be something in it, so that mere condemnation is unconvincing. On another page Dr. J. C. Brocklehurst describes some experiments arranged to test the deodorant action in an objective way. He used methylmercaptan as a substance with an unpleasant odour. It is said to be present in the urine after eating asparagus, and its relation, vinylmercaptan, is the substance discharged by the skunk. Dr. Brocklehurst showed that, when methylmercaptan passed a screen of filter-paper soaked in chlorophyll solution, it reduced just as much iodine as when the screen of filter-paper was soaked in water, showing that the methylmercaptan was not destroyed by the chlorophyll. Thus he substituted a quantitative estimate for an olfactory impression. He then bubbled nitrogen carrying methylmercaptan through a chlorophyll solution on the one hand and through water on the other and again failed to observe any difference in the decolorization of iodine. Another series of experiments revealed a deodorant action in one out of 22 trials, though here Dr. Brocklehurst regarded the mercaptan smell as merely being masked by a very strong smell of the chlorophyll solution. Observations were also made on a patient with incontinence of urine and faeces, and on a normal subject who ate asparagus. In neither of these was there any modification of the smell of the urine when large amounts of chlorophyll preparations were taken.

Recently Dr. A. H. Corwin,[2] head of the department of chemistry at Johns Hopkins University, quoted to the American Chemical Society a report from the National Bureau of Standards which said that "we have no reason whatever to believe that chlorophyll has anything to do with deodorization." It is evident that the wave of credulity which has swept the United States has not overwhelmed everyone, and it is to be hoped that it will not overwhelm too many in Britain. Some who are sceptical of chlorophyll tablets have faith in appliances which allow a substance to evaporate from a wick, the wick standing in a solution which contains chlorophyll; this substance is said to remove odours. Crotonaldehyde has been used for this purpose, and like formaldehyde it renders the olfactory nerve endings less capable of detecting any odour, unpleasant or otherwise.

NEW CORONERS RULES

New Coroners Rules came into force on March 1. They largely embody the B.M.A.'s recommendations, which were submitted to the Coroners Rules Committee of the Home Office in April, 1951.[1]

Rule 26 provides that proceedings at an inquest shall be restricted to finding out who the victim was, how, when, and where he died, if the cause of death was murder, manslaughter, or infanticide, who ought to be charged as principal or accessory to the crime, and the particulars required for registration. Neither coroner nor jury is to express an opinion on anything else, except that they may make a recommendation designed to prevent a recurrence of similar fatalities. No rider to any other effect is to be recorded by the coroner. This

[1] *British Medical Journal*, 1952, **2**, 1086.
[2] *Sci. Amer.*, 1953, **188**, 38.

[1] *British Medical Journal Supplement*, 1951, **1**, 159.

should go some way towards eliminating the cross-examination whose real purpose is not to ascertain the cause of death but to prepare the way for an action for damages against someone who may be civilly liable. It is reinforced by Rule 33, which expressly provides that no verdict is to be framed in such a way as to appear to determine any question of civil liability.

If anyone's conduct is likely in the coroner's opinion to be called in question at the inquest, he is to be either summoned to give evidence or given notice of the date, place, and time when it will be held. Further, if in the course of the inquest someone who is not there, and has not thus been given notice, has his conduct called in question on grounds which are substantial and relevant, the inquest must be adjourned to enable him to be there if he wishes. This will prevent anyone from being criticized without having the opportunity to give evidence on his own behalf. By Rule 18 the rule of evidence in legal proceedings both civil and criminal, that no witness has to answer a question tending to criminate him, is expressly applied to inquests. By Rule 28 documentary evidence is not to be admitted without the matter of the document being called, unless the coroner is satisfied that there is a good and sufficient reason why he should not attend; and, once it is admitted, if the coroner or any other properly interested person so requires, the inquest must be adjourned to enable the maker of it to give oral evidence. By Rule 16 the police are entitled to examine witnesses only through the medium of a solicitor or counsel. In all these matters of evidence the tendency of the Rules is to bring proceedings at an inquest more nearly in conformity than they have been in the past with proceedings in court. By Rule 8, although the full B.M.A. recommendation is not met, it is provided that necropsy is not to be carried out in a dwelling-house or on licensed premises, but only in premises adequately equipped for the purpose with running water, proper heating and lighting facilities, and containers for storing and preserving what may be necessary. It is satisfactory to find that these important provisions in the new Rules so largely accord with the Association's recommendations.

THYMECTOMY AND MYASTHENIA GRAVIS

In an article in the *Archives of the Middlesex Hospital* (which has maintained a high standard since its welcome reappearance two years ago), Holmes Sellors[1] has reviewed the treatment of myasthenia gravis by thymectomy and described the results of the operation in 37 cases: 32 of these patients had symptoms of myasthenia gravis. He concludes that removal of the thymus offers the best hope of permanent relief in this disease, particularly if carried out in its early stage. The connexion of the thymus gland with myasthenia, and indeed its function in the normal individual, remain unknown. That the thymus often appears enlarged or may contain a tumour in myasthenic patients was observed at necropsies fifty years ago. Sauerbruch carried out partial removal of the gland in 1911, but no further attempts to relieve the disease in this way were made until Blalock's work in Baltimore; he published[2] the results of 20 operations in 1944. Since then the operation has not found as great favour in the U.S.A. as it has in this country, where the results in 155 cases published by Keynes[3] in this *Journal* have been most stimulating. Over 90% of the surviving patients in his series were improved.

Most patients with myasthenia gravis have been treated with neostigmine since Walker,[4] in 1934, reported on the relief of symptoms afforded by this drug. It is usually effective by mouth, but sometimes must be given by injection: atropine may be necessary to neutralize the side-effects, such as abdominal griping. Neostigmine must usually be taken after thymectomy, but often in smaller doses than before, and it becomes more effective. Some patients are so much improved that they dispense with it altogether. Sellors, like Keynes, has found that the operation is most likely to be successful when the history is short, and that, even in patients greatly benefited in other ways, muscles which have been weak for a long time may not recover, so that ptosis, for example, may be permanent. Some patients do not improve at all; unfortunately no way of predicting the likely result in any individual has been found.

About one in ten myasthenic patients has a tumour of the thymus, benign or malignant, though not all thymic tumours are associated with myasthenia. Some may be symptomless, and others may cause mediastinal obstruction. The tumours may be impossible to diagnose before operation, even with careful radiography. Sellors and Keynes have both found that the prognosis is poor after operation in cases of myasthenia with a tumour of the thymus, for the condition is liable to relapse. Occasionally the thymic tissue is ectopic, lying in the first or second intercostal spaces, but usually it is found immediately beneath the sternum, as in the infant, and consists of two lobes united by an isthmus, closely related to the left innominate vein. Surgical access is provided by vertical division of the sternum. All thymic tissue must be removed, and this is ensured by leaving no visible fatty tissue in the anterior mediastinum. If there is a tumour, adjacent pleura or pericardium should be excised: with controlled respiration by endotracheal anaesthesia no harm results, but wound closure must be airtight. Post-operative pulmonary complications can be dangerous, since muscular weakness may make coughing or even breathing difficult. Neostigmine should be continued, and it is wise to have an artificial respirator, such as a Drinker's apparatus, to hand. A watch should be kept for pneumothorax, and aspiration or bronchoscopy may have to be carried out if secretion of mucus becomes excessive or if atelectasis occurs. Some patients improve immediately after operation, others improve gradually. In its natural course the disease fluctuates in severity and there may be long remissions. These must be allowed for in assessing results of treatment, but, even so, Sellors's report confirms the value of operation.

[1] *Arch. Middlesex Hosp.*, 1952, 2, 1.
[2] *J. thorac. Surg.*, 1944, 13, 316.
[3] *British Medical Journal*, 1949, 2, 611.
[4] *Lancet*, 1934, 1, 1200.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

MEDICAL ASPECTS OF AIR TRAVEL—I. ENVIRONMENT AND IMMUNIZATION REQUIREMENTS

BY

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Now that travel by air has become so commonplace general practitioners are consulted more and more by their patients on its medical aspects. The points on which information is often wanted are the medical contraindications to flying, how babies and the elderly react to long flights, what facilities are available for invalids, and what are the immunization requirements.

First, it is desirable briefly to consider the environment, particularly the limitations of space and other facilities on an airliner, and the effects of speed, altitude, noise, and vibration, as these are all factors of importance in the care and comfort of invalids who contemplate travelling long distances.

Space and Facilities for Invalids

The space allotted to each passenger is relatively small, even in the most luxurious airliners, and is virtually limited to a seat. Under the best conditions reclining seats are in pairs, with an arm-rest between them, arranged in rows on either side of a narrow gangway 18 to 20 in. (46 to 51 cm.) in width. Each pair of seats is pitched some 39 to 46 in. (99 to 117 cm.) from the next pair, so that there is just room to get in and out past one's neighbour. In some aircraft a number of sleeping berths can be made up at night. There is, of course, an extra charge for these, as there is also for any stretcher space needed; in the latter instance the charge is usually double fare, as two seats are occupied.

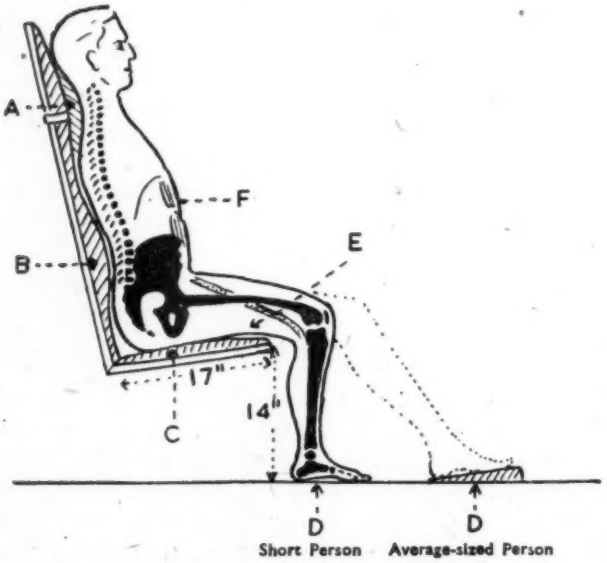


FIG. 1.—Diagram showing anatomical points in aircraft seats. (A) Adjustable support for head and neck. (B) Padding to support small of back. (C) Compression of seat cushion should not exceed 1 in. (2.5 cm.). (D) Feet must reach floor to take weight off lower thighs. A footstool damps vibration. (E) Avoid pressure on main veins and lymphatics and so prevent swelling of feet and ankles. (F) Position prevents abdominal muscles being too relaxed and so lessens pooling of blood in large veins of abdomen and helps to avoid flatulent distension of the gut.

Comfortable seats are essential on long flights of six to twelve hours at a stretch, otherwise passengers cannot rest properly, become unduly fatigued, and suffer from discomfort in the small of the back and from postural oedema of the feet, especially if they have poor circulation. This oedema is largely the result of the seat being too soft and too long in the pan, so causing widespread pressure on the veins and lymphatics of the buttocks and underside of the thighs. The backache is due to insufficient support in the back of the seat to maintain the proper curve of the lumbar spine, with the result that the ligaments and muscles concerned are overstretched. Nowadays many aircraft seats are constructed on sound anatomical and physiological principles (Fig. 1), with padding in the right places and tilting devices to enable passengers to adjust their position from upright to reclining and with feet raised enough to prevent oedema. In addition, footstools and soft cushions are available to give further support where required and to suit individual peculiarities of build.

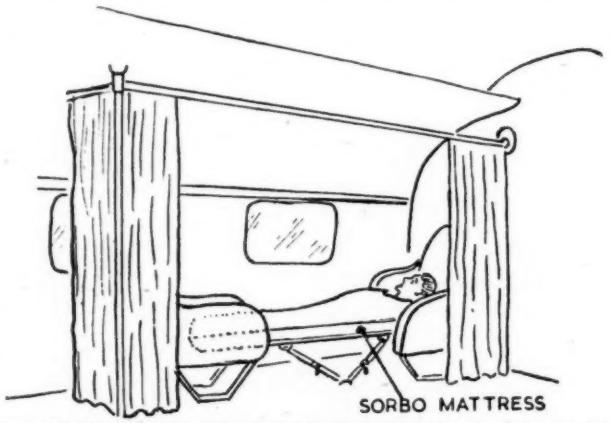


FIG. 2.—Stretcher cot suspended between two chairs and fastened to floor.

Where necessary or advisable, the airline's medical department recommends acceptance of certain types of invalids as stretcher or sleeping-berth cases only. Special seats are then allotted for the purpose, so that a stretcher can be accommodated or a lie-down constructed by bridging the gap between two facing seats and covering this with a mattress (Fig. 2). Curtains are available to screen off these invalids, particularly those requiring dressings or special attention during the flight.

Toilet facilities in a 40 to 60-seater aircraft are limited to a small "powder room" with two wash-basins and one closet for ladies, and a lavatory with two or three wash-basins, a urinal, and a closet for men. Hot meals are served in flight or at stopping places *en route*, and special diets can be provided for invalids if notification is given in advance.

Speed and Smoothness of Flight

Speed is not felt in the cabin type of aircraft so long as it is uniform and there are no visual cues, such as passing-by objects like clouds. Alterations in the speed or direction

of the aircraft, however, are felt: the greater the degree of change the more the sensation. Commercial passenger-carrying aircraft are flown so as to cause little or no sensation of speed; in fact, the only time when speed may be appreciated at all is at take-off and during ascent and descent, and even then it is no greater than that experienced in a carefully driven motor-car. Some motion may be felt in "bumpy" weather conditions, especially when flying through cloud, and this may cause airsickness in predisposed individuals. Bad-weather clouds frequently extend up to altitudes of 15,000 to 25,000 ft. (4,600 to 7,600 metres) in temperate zones and to 40,000 ft. (12,000 metres) or more in the Tropics. Modern airliners have therefore been specially designed to fly smoothly and speedily (up to 500 m.p.h.—800 km.p.h.) at altitudes between 15,000 and 40,000 ft. (4,600 and 12,000 metres)—that is, 3 to 8 miles high—and to do this the aircraft has to be "pressurized."

Effects of Altitude

Oxygen Lack or Anoxia

Although the air has the same percentage composition of its component gases at any altitude within the earth's atmosphere, it becomes progressively rarefied with increasing altitude above sea-level in accordance with Boyle's law. At 18,000 ft. (5,500 metres) the air has half the density it would have at sea-level, and at 40,000 ft. (12,000 metres) about one-fifth. This gives a rough idea of the corresponding reduction in the partial pressure of the oxygen available in the air inhaled at different altitudes. Healthy individuals are less affected by lack of oxygen than are the non-robust. The onset of anoxia in flying is insidious, and the symptoms are very similar to those of alcoholism: the individual is oblivious of the fact that he is suffering from lack of oxygen, and, like the inebriated, feels that he is "on top of the world" even when "half under the table." The first symptoms of oxygen deficiency of relatively minor degree occur after a stay of over an hour at an altitude of 10,000 ft. (3,000 metres), but normal individuals and most invalids, if more or less sedentary, can remain in the atmosphere of an altitude of 8,000 ft. (2,400 metres) for ten to twelve hours without suffering anything more than the ennui and fatigue experienced in most modes of travel. Aircraft are therefore pressurized to a degree adequate to compress the air in the cabin (even when the aircraft is flying at an altitude of 40,000 ft.—12,000 metres) to a density of the air at an altitude of 8,000 ft. (2,400 metres) or lower and to maintain it constantly at that density. When invalids are carried, however, the precaution is taken to provide special oxygen sets in case of need, but in practice it has been found that these are seldom required.

Air and other gases contained in the body spaces—for example, the middle ear, the paranasal sinuses, and the alimentary tract—naturally are also subject to Boyle's law, and therefore expand and contract with decrease and increase of the atmospheric or cabin pressure.

Ventilation of the Middle Ears

Normally, the air pressure on either side of the eardrums is equalized automatically by the expanding air escaping from the middle ears by way of the Eustachian tubes during ascent and by being drawn in during descent. This ventilation of the middle ears is apt to fail if the Eustachian tubes are even only partially occluded by nasopharyngitis or some other condition affecting their apertures, especially during a rapid descent, as the continuing contraction of the air imprisoned in the middle ears tends to draw together the walls of the Eustachian tubes. Consequently the tympana are drawn in and congestion or even rupture of these membranes may result (acute otitic barotrauma). The immediate symptom is acute earache, followed by some loss of auditory acuity and sometimes by tinnitus and vertigo. These symptoms may persist for some hours after ventilation of the ears has been re-established by the Valsalva technique or, in severe cases, by puncture of the safe area of the tympanum with a fine needle. It follows, therefore, that those suffering from acute nasopharyngitis or sinusitis should be advised not to fly until they have recovered; if they do fly with a head cold they should inhale amphetamine or some other vasoconstrictors to help clear their Eustachian tubes.

Descents in airliners or alterations in their cabin pressure are usually made very gradually to permit proper ventilation of the middle ears, even if the passengers are sleeping. Young children may get airlocks in their ears: this makes them cry, an act which immediately relieves the condition by opening their Eustachian orifices. Mothers with babies should be instructed to give them a feed or a dummy to suck during ascent and descent. Persons about to travel by air for the first time, and who are apprehensive of their ability to ventilate their middle ears, should be advised to suck a sweet, chew gum, or practise the Valsalva technique during ascent and descent. In fact, this is a wise precaution for all to take, and it is the custom for cabin attendants to hand round to every passenger boiled sweets or chewing-gum at appropriate times.

Gases in the Alimentary Tract

Expansion of gas in the gut usually causes no trouble, except the embarrassment of passing flatus. It may, however, create painful distension in those with lax abdominal walls, and may even be dangerous on account of haemorrhage or perforation in cases of active ulceration or after major operations on the stomach or intestines. The general rule, therefore, is not to accept for air travel cases of appendicectomy or herniotomy for ten days after operation, and those who have had gastrectomy or a perforation or haemorrhage of the stomach or intestines (except for haemorrhoids) for at least two months after the event. Colostomy cases are usually not acceptable in the confines of an aircraft, owing to the odour from escaping faeces and flatus. Distension of the stomach and intestines may embarrass those with certain heart and lung conditions by interfering with diaphragmatic movements. Usually, however, alimentary tract distension is automatically relieved by the passage of flatus. It is in the interests of those prone to flatulence to ensure a good evacuation of the bowels before flight, to abstain from gas-producing foods (legumes and excess of carbohydrates), to avoid overeating during the journey, and to absorb some of the gas by means of charcoal biscuits.

Noise and Vibration in Aircraft

Noise and vibration of certain frequencies and intensities if continued are disturbing, induce fatigue, and contribute to the onset of airsickness, all of which are apt adversely to affect invalids. Most of the noise and vibration experienced when flying is derived from the engines, though some is from aerodynamic turbulence over the skin of the aircraft. Modern airliners are designed to reduce these defects as far as practicable by using sweeter running engines, by efficiently muffling and orientating exhausts, and by soundproofing cabins. These measures have proved most effective in jet and turbo-jet aircraft, especially in the former, owing in part to the absence of propellers and pistons and in part to the fact that the engine noise is mainly of high pitch, which is more readily damped down or cut out by soundproofing than is the lower-pitch noise of the piston engine. Cotton-wool is handed out in all aircraft so that those susceptible to noise can plug their ears; alternatively, passengers can provide themselves with rubber ear-plugs, but these are no more effective than moistened cotton-wool. Such plugs are not really needed in jet and turbo-jet aircraft, which are as quiet as most saloon cars.

Airsickness

It is appropriate now to consider airsickness, or motion-sickness, as a number of predisposing factors have already been mentioned—namely, bumpy weather, oxygen want,

fatigue, flatulence, noise, and vibration. Airsickness is rare in pressurized aircraft, which fly above the weather: in fact, the incidence is about 0.6% of all passengers carried, and even then it is usually only a temporary occurrence during ascent and descent when flying through cloud or regions of changing air temperatures in warm climates. It is important, however, to safeguard invalids against airsickness, particularly diabetics, pregnant women, and those with gastro-intestinal lesions such as ulcers and post-operative conditions.

Fortunately, airsickness can be prevented in most cases by the simple expedient of swallowing 1/100 gr. (0.65 mg.) of hyoscine hydrobromide half an hour before the time of take-off. Children under 15 years of age should be given half this dose. (Incidentally, hyoscine has been proved by the U.S. Air Force to be more efficient as a preventive of airsickness than the antihistaminic drugs.) It is rarely necessary to repeat the dose, as acclimatization to aircraft motion develops quickly in most instances, especially if steps are taken to minimize other predisposing factors. It is advisable, therefore, for invalids to be well rested before and during the journey, to obtain a good evacuation of the bowels before flight, to keep comfortably warm, and to plug their ears with cotton-wool to lessen noise.

Motion is felt less near the centre of the aircraft than towards the tail, so seats for invalids are specially allotted. Those who are particularly susceptible to travel-sickness should relax, lie back in their seats, and look upwards, so as to prevent over-stimulation of the labyrinths.

Immunization Requirements

In accordance with the International Sanitary Regulations of the World Health Organization, which came into force on October 1, 1952, passengers undertaking international air travel have to be in possession of certain immunization certificates, depending on the place of departure, the countries of transit, and the destination. For most journeys the would-be traveller must have been vaccinated against smallpox within three years, and, if it is intended to pass through or leave a yellow fever zone, immunized within six years against that disease. When travelling from or through cholera endemic areas, inoculation with anti-cholera vaccine is necessary within a period of six months. The immunizations done must be recorded on the international vaccination certificate form prescribed by the World Health Organization, dated* and signed by the doctor doing the inoculations, and in the case of yellow fever vaccine its origin and batch number must be stated.

Each certificate must then be authenticated and stamped by an authority approved for the purpose by the health administration of the particular country—that is, the Ministry of Health so far as England and Wales are concerned. The approved authenticating authority in England and Wales is the health officer of the town council, urban district council, or rural district council in whose area the doctor practises. These certificate forms are obtainable from the airline company or travel agency concerned or from the Government health department, except those for yellow fever vaccination, which are held at certain recognized centres. Details of immunization requirements can be obtained from the medical or traffic department of the airline concerned, or from the embassies, consulates, or other Government representatives of the countries to be visited. It is most important that travellers should have these certificates completed in all details and have them available with their passports throughout their journey, otherwise they are liable to be subjected to delays, compulsory vaccination, or surveillance, detention in quarantine, or to a fine.

Vaccination against smallpox and yellow fever should not be done at the same time, especially primary vaccination, as this increases the risk of encephalitis. Vaccination against yellow fever should always precede that against smallpox, because if primary vaccination were done first there would have to be an interval of twenty-one days before giving the yellow fever vaccine. A convenient scheme of inoculations, when all are needed, is as follows: First day: vaccination against yellow fever, cholera, and typhoid group (first T.A.B.); fourth day: vaccination against smallpox; seventh to ninth days: second dose of T.A.B. vaccine, after reading and recording the result of primary vaccination.

If it is decided that it is best for medical reasons not to give a required vaccination, the doctor concerned must certify the fact. It must be appreciated, however, that such individuals may be refused entry into certain countries or be detained in quarantine, and that the airline carrying such persons may have to remove them from the country at its own expense or pay a fine, and the aircraft may be detained. In any case a form of indemnity must be signed by a person who proposes to travel without any necessary certificate of vaccination: this is required to free the airline from any liability if the passenger meets with difficulties or expenses *en route* or on arrival. Conscientious objectors to vaccinations are treated in the same manner as those without valid certificates.

[Part II will appear in our next issue.]

*The date should be written thus, 3/X/52, to prevent misunderstanding, as in some countries the month is recorded in front of the day.

Nova et Vetera

AN EARLY CASE OF HAEMOLYTIC JAUNDICE OF THE NEWBORN

During the last few years light has been shed on the condition whereby newborn infants used to perish in a deeply jaundiced state within a few days of birth; before the discovery of the Rhesus factor in the blood and its significance for the infant the occurrence of fatal jaundice which started soon after birth was a sad and hopeless problem. Lately, in searching through some letters written to Sir Hans Sloane and now preserved in the British Museum, one was found which is of historical significance and which, by the kindness of the authorities of the Museum, I am able to reproduce here. It was written to Sir Hans by Dr. George Cheselden, of Leicester, probably a distant relative of William Cheselden. It is dated Leicester, February 25, 1729, and runs as follows:

"At the request of a patient of mine (the bearer) I give you the following short account. The case of the gentlewoman has been very extraordinary. She has had the misfortune to lose 3 fine boys who came into the world with very healthful symptoms for the first 2 days and then the strongest signs of an icterus appear'd the epidermis being all over tinctur'd alike which bad symptoms prov'd most certainly mortal in a few days medicine being of no service to the infants.

"The mother for the generality has good health even when with child only, give me leave to observe that a few days after her quickening her water changed into a true jaundice colour as high as possible and so continues till she is deliver'd, and then as well as usual. Evacuations of all kinds we have made use of in vain alteratives chalybeates and advis'd to no purpose. Last year I advis'd to Scarborow with no better success.

"The last child to all outward appearance was a healthful one excepting the febrick disorder. I therefore importuned the parents that I might examine the Vesica Fell. Ductus Communis in which we found nothing amiss, all the viscera intirely perfect the liver not larger nor harder than common no stone nor obstruction anywhere nor decay in any part nor any part emaciated. The mother's habit of body you'l be better able to judge than I can represent in any letter. I hope that you'l be so good as to put the lady into a more successful method which I do assure you will give a great deal of satisfaction to

sir, your most obedient and humble servant

GEORGE CHESELDEN.

"P.S. One line will be esteemed a favour."

There is no record of the reply from Sir Hans Sloane, but it is to be feared that it would not have contained any solution for the problem propounded. V. Z. C.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Assistance for Doctors in Flood Areas

SIR,—You kindly published my letter in the *Journal* (February 14, p. 399) in which I appealed to members of the profession to send donations to the Sir Charles Hastings Fund in order that the Trustees might give some immediate assistance to those doctors who have suffered in the recent floods. The response to my appeal has been most gratifying, and through the generosity of certain local medical committees and many individual members of the profession a sum of £1,200 has been received. In addition, through the Canadian Medical Association, our colleagues in Canada have most generously sent a splendid gift of $1,000. Furthermore, the Trustees of the General Medical Services Defence Trust have very kindly decided to make available to the Trustees of the Hastings Fund moneys for immediate assistance up to £5,000 as and when necessary. As a result of this response the Trustees have been able to make gifts to certain doctors who have sustained considerable loss and whose houses have been severely damaged as a result of the flood waters.

The Trustees are anxious to give all further assistance that may be needed and hope that all doctors who have suffered on account of the floods, or anyone knowing of their difficulties, will not hesitate to write to the secretary to the Trustees. The question of long-term arrangements with regard to individual practices in these areas is already under discussion between representatives of the General Medical Services Committee and the Ministry of Health.

May I repeat that contributions should be sent to the secretary of the Fund at B.M.A. House, Tavistock Square, London, W.C.1, cheques being made payable to the Sir Charles Hastings Fund, and the envelopes marked "Flood Relief."—I am, etc.,

London, W.C.1. E. A. GREGG, Chairman of Council.

Ciba Foundation's Colloquia on Endocrinology

SIR,—In his pleasant review of four volumes of the Ciba Foundation's *Colloquia on Endocrinology* (February 21, p. 440) Dr. C. L. Cope commented that "it is disturbing to find that about two years have elapsed between the holding of many of these colloquia and their appearance in book form. . . . Speedier methods of publication must be found if these reports are adequately to serve the purpose for which they are intended."

In fairness to our publishers, I should like to explain that the unfortunate delay in some of these instances was due in part to my failure to anticipate the demand for publication of the earliest informal meetings, in part to my inexperience in having the whole of the proceedings of these first conferences electrically recorded, with all that that meant in later transcription—a hard lesson—and in part to the fact that, when meetings are held of people from distant parts of the world, texts of the general discussions and proofs of papers have later to be sent equally far afield for correction—one contributor alone has held up publication of a volume now in the press for four months. Further, I should mention that the first of the volumes reviewed by Dr. Cope was published ten months ago.

So far as "speedier methods of publication" are concerned, I should point out that it is never intended that the conferences held at the Ciba Foundation should provide occasions for the announcement of completed research; rather we prefer to discuss problems in current research, and any value in the subsequent books is mainly due to the collection within one cover of facts and thoughts published, or about to be published, elsewhere, but scattered throughout the world's literature.

The time taken over some of the volumes now in the press will, we believe, compare not unfavourably with the delay in publication of articles in some of the best-known special journals. The fact that our book *Isotopes in Biochemistry* was published in less than seven months shows how excellently our publishers, J. & A. Churchill Limited, carry out their side of the business when given the chance.—I am, etc.,

London, W.1. GORDON WOLSTENHOLME, Director, Ciba Foundation.

The Backward Child

SIR,—I agree with Dr. Brian H. Kirman (February 7, p. 334) that as a rule it is undesirable to classify pre-school children as "ineducable." Moreover, where an occupation centre is not available, as in many parts of the country, and the child is attending the infants' class of a school, and the teacher is satisfied with his behaviour, classification and notification are not indicated either.

The terms "educable" and "ineducable" do not separate children into watertight compartments, but must be interpreted not only in the social setting but in the light of advances in psychology and education. The latter is clearly veering away, although slowly, from a mechanistic philosophy. Theoretically, at least, secondary education is conceived not as a separation of the "superior" and "inferior," but as a differentiation into qualitatively different cultures.

In Glasgow, where I practised for some years, the term "special" has been abandoned in the designation of schools for "educationally subnormal" children. Since the modern "occupation centre" provides a wide range of stimulus patterns for the varied interests and levels of insight of relatively retarded children, whose response to adequate stimulation is obvious, it merits *par excellence* the generic title of an educational establishment—that is, school.—I am, etc.,

Perranporth. D. JACKSON.

Christmas Disease

SIR,—Dr. Rosemary Biggs and her colleagues are to be congratulated for their excellent article (December 27, 1952, p. 1378). In this important paper it is pointed out that two individuals, both exhibiting clinically indistinguishable evidence of haemophilia, may actually lack two quite different substances from their plasma. The methods used and the results obtained are the same as those reported earlier in 1952 by Schulman and Smith.[1] The purpose of this letter is to protest against the name "Christmas disease" which has been adopted by Biggs *et al.*, because this name suggests a holiday rather than a haemorrhagic blood dyscrasia.

Since the patients exhibit a syndrome having haematological, clinical, and genetic features identical with those of classic haemophilia, it is not clear why the diagnosis of haemophilia is not applicable to these patients as well. As the authors point out, at least two substances exist in the plasma, a deficiency of either of which can give rise to a haemorrhagic disease. If these substances are designated by the numbers I and II, respectively, then the two corresponding haemorrhagic diseases could be designated as haemophilia I and haemophilia II, the former referring to the more commonly occurring type. Since at least two varieties of haemophilia exist, there is a possibility that there may also be a third or a fourth variety. This simple terminology, which is similar to that used by Schulman and Smith in their article, would allow for possible expansion should this become necessary as a result of future investigations. In the letter by Dr. Biggs and her colleagues (January 24, p. 221) the possibility of names such as haemophilia A and haemophilia B (or haemophilia I and haemo-

philia II) is discussed but rejected. The authors argue that the designation should emphasize the differences in the disease. However, all advances in scientific knowledge have always depended on the discovery of universal laws governing seemingly dissimilar phenomena, and, in fact, biological classifications are based primarily on similarities rather than on differences. Probably haemophilia I and haemophilia II (or haemophilia A and haemophilia B) are transmitted by corresponding allelic sex-linked genes (h^A and h^B). In this connexion it is of interest to notice the appearance of an article containing evidence of still another allelic form (h^m) of haemophilia.[3]

These remarks must not be misconstrued as evidence that the undersigned considers differences unimportant. In fact, two important sciences, genetics and blood grouping, arose entirely from the study of individual differences. In the designations haemophilia A and haemophilia B the existence of differences is clearly indicated by the letters, and at the same time proper emphasis is placed on the fact that these are both haemorrhagic blood diseases. In the name "Christmas disease," on the other hand, any emphasis is completely misplaced.—I am, etc.,

Brooklyn, New York. A. S. WIENER.

REFERENCES

[1] *Blood*, 1952, 7, 794.
[2] Graham, J. B., *et al.*, *Amer. J. med. Sci.*, 1953, 255, 46.

Mental Hospital Service

SIR,—The Minister of Health is reported (*The Times*, February 6) to have said at the annual conference of the National Association for Mental Health that 8,000 persons, including a large number of children, are awaiting admission to mental hospitals. It is not possible to be sure how many patients are awaiting admission to mental hospitals proper, but it is certain that the majority of mental hospitals are overcrowded, some grossly so, and that many potential voluntary patients are being denied the help that in-patient treatment could give. There are many reasons for this. The poor facilities for the proper classification of patients due to overcrowded and out-of-date buildings are one important reason. Cases of psychoneurosis are too often mixed with psychotics in the same ward. Perhaps the most telling reason of all must be the inability of the average medical and nursing staff of a mental hospital to deal with any great number of voluntary patients suffering from neurosis or psychoneurosis. Psychiatrists know that the starting of a vigorous out-patient department soon greatly increases the number of voluntary admissions—a measure of a state of great and still largely unrelieved mental suffering in the community. Providing for the treatment of great numbers of early psychotic and neurotic patients requires careful consideration and planning if we are not to make serious mistakes.

The clinician working in a mental hospital is faced with two main clinical problems; first, the care of a large population of chronically mentally ill patients, most of whom will never leave the hospital, and, secondly, the active treatment of the new cases, usually at the rate of some hundreds a year. The way to avoid overcrowding and the frustration of being overwhelmed with both chronic and acute patients is not necessarily to provide still larger and more elaborate buildings. The two things that would do more than anything else to lessen the problem of mental illness would be to pursue an energetic programme of clinical treatment to prevent patients becoming chronic, and to provide adequate domiciliary and aftercare services for patients who have left hospital. We are convinced that the number of chronic patients being produced every year can be greatly lessened. It requires only the right sort of will and the necessary time and skill. Pinel managed it 150 years ago, with no "modern forms of treatment" (Pinel, P., *A Treatise on Insanity*, 1806).

We would submit some suggestions for improving the present state of affairs. In the hospitals themselves it would be better to spend money on providing more psychiatrists, particularly those skilled in psychotherapy and group therapy, rather than on providing new buildings and more beds. Junior staff are just as important, and every mental hospital should have its own registrars and carry out its own psychiatric training. In connexion with this, far more regional facilities for taking the D.P.M. are required. Occupational therapy should be developed towards providing active rehabilitation for acute and recent cases rather than for providing occupation for chronic patients. The services of social workers need to be vastly extended, and their training should be based on the mental hospitals, so that psychiatrists can have the kind of service from them that they really need. Outside the hospitals, training centres exclusively for ex-patients and out-patients are greatly needed, as also is the need for group therapy at out-patient clinics. Perhaps the greatest single need is for psychiatric out-patient clubs, not run as a means of recreation for chronically mentally infirm patients, but staffed by one or more psychiatrists and a team of social workers and designed as active treatment units. Such clubs would, in our opinion, greatly reduce the number of readmissions—those dismal evidences of our failure who lower morale among both patients and staff.

A final word about "neurosis centres." These could be cheaply built on the lines of the many wartime hutted hospitals. The psychiatrists who oppose neurosis hospitals do so on the grounds that the mental hospitals will then only receive chronic patients. This difficulty could be overcome if the neurosis units were administered by the medical superintendent. This control could extend to neurosis beds in general hospitals. Every mental hospital would then have, in effect, three types of admission wards—one for the neurotic and early psychotic patients, the second for disturbed psychotics, and the third for elderly psychotic and demented patients. If neurosis centres are not allowed to become independent, nobody need fear that all the interesting and recoverable cases will pass out of the hands of the mental-hospital psychiatrist.

Our problem is, and will be for a long time to come, that there are already far too many patients for us to have time to treat properly. We would suggest that the Minister should consider the setting up of a small national committee to design a plan for the future of the mental hospital service.—We are, etc.,

R. A. SANDISON.
Worcester. A. M. SPENCER.

The Metric System

SIR,—Dr. C. Langton Hewer's purist (February 21, p. 450) would be quite correct to speak of his blood count as 5 million per cubic millimetre, and at the same time to hold up his hands in horror if one referred to, say, his output of urine in cubic centimetres. This is because the volume of diluted blood in the haemocytometer chamber is based on linear measurements and so is correctly expressed as a unit of length cubed, whereas measures of volume like the litre are not.

The original idea of the French Government was to have all measures of length, volume, and mass based on a natural standard or metre—the ten-millionth part of a polar quadrant passing through Paris. Difficulties, however, led to an artificial standard metre being adopted and then an artificial standard of weight, the kilogram, not based on the metre. The unit of volume or litre was defined as the volume of a kilogram of water. As this kilogram is not strictly related to the metre the thousandth part of a volume of water of equal weight is not related to the metre either. It is not a cubic centimetre but is called an ml. (Incidentally the word "mil" is an engineering term for the thousandth part of an inch, now generally referred to as a "thou.")

Dr. Hewer's objection that 3.55 ml. per 6.35 kg. is hard to remember is not really a serious one. Surely doses are not so strict as all that and an expression in terms of the nearest ml. and round kg. would serve.—I am, etc.,

Enfield. C. ALLAN BIRCH.

SIR,—With reference to your leading article on the metric system (February 7, p. 320), may I say that the older system is actually very safe and convenient in practice; that Professor W. C. W. Nixon and Mr. T. D. Whittet (p. 327) very much underrate the difficulties in making a complete change; and that, so far as I know, the Association has never committed itself to the policy you advocate.

I am, however, much more concerned to point out what the older system of weights and measures actually did. In the days when counting was not so common as it is to-day different names were given at small intervals for the

measures most commonly in use, with units above and below these at much wider intervals. This holds broadly for weights, and measures of length and capacity. In fact, though many intermediate measures such as ell, gill, etc., were used, our forefathers had produced something like a logarithmic scale on either side of the common mean. This may not suit the age of comptometers and mechanization, but it was adapted to the needs of the time, it was a fumbling after something even more advanced than decimalization, and it minimized the chance of errors (which are very serious with decimal points). It ill becomes doctors to forget that measures were made for man and not men for machines.

The change-over may be inevitable, but let us credit our ancestors with possessing a sense of proportion which your article and that of your contributors signally fail to show when they compare the change-over in helm orders—which from the nature of the case had to be done universally at a given time—with a change which entails the re-marking or scrapping of most of the weights, measures, and containers in most of the dispensaries and chemists' shops in this country.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

The General Practitioner and Mass Radiography

SIR,—May I correct any false impression that it is universal practice to disallow general practitioners direct access to *x*-ray departments for the radiological investigations of their patients? The services of the *x*-ray departments under my charge have been available to general practitioners for the past five years. In the case of simple chest skiagrams, patients are *x*-rayed and reports reach the practitioners within a few days of the request being made. This is the routine practice, but where it is indicated that a more urgent examination is required suitable arrangements can be made to meet the needs of the case. In addition to the above service one of the hospital *x*-ray departments is also providing facilities for the *x*-ray examination of every case referred to the chest clinic, since the latter is housed in the main hospital building and has no independent radiography unit of its own. The area concerned has a population of 200,000.

Before, therefore, embarking on the scheme proposed by Dr. F. A. Nash and his colleagues (February 7, p. 304) consideration should be given to the possibility of getting freer use, for all interested parties, of the facilities which the main *x*-ray department of the hospital can provide. This service would, of course, be additional to the periodic surveys of the mass radiography unit.—I am, etc.,

Halifax. R. I. LEWIS.

SIR,—I was pleased to see prominence given recently to routine diagnostic chest radiography services for general practitioners, both in the article by Dr. F. A. Nash, Mr. B. Benjamin, and Dr. T. J. Lee (February 7, p. 304) and in your annotation (p. 322). In particular the conception of relatively minor symptoms possibly representing early pulmonary tuberculosis is of considerable importance and can always bear repetition. Diagnostic delay is still all too common because radiographic action is not taken on symptoms alone, as it should be. Accepting that routine radiography on suspicion can go a long way to improve this position, the problem is how to provide the necessary radiographic facilities. In many areas a service similar to that described is being provided by the chest clinics in spite of the increased work thrown upon them by the shortage of sanatorium beds and the increased use of the clinics by practitioners for routine consultation on pulmonary problems. This suggests that the chest clinic fulfils a very real need, and in my opinion the time has come to consider whether the population (often 200,000–300,000) served by individual chest clinics is not very much too big.

The modern chest clinic is providing important and widely appreciated facilities which are becoming increasingly used. This service could be much more efficient were the population served by each clinic (as at present constituted) considerably smaller—certainly not larger than 100,000 in urban areas. It would then also be possible for routine diagnostic radiography for general practitioners to be undertaken more easily. There is a much greater "recall" rate with such schemes than with routine mass miniature radiography as at present practised, and it is logical that chest clinics should undertake the work in such circumstances. Odelca camera units in chest clinics would facilitate this, and they have already been installed with considerable success in a number of clinics. Existing mass miniature radiography units could thus be used for the larger scale mass surveys in "black" areas which are still needed. Later, or at present if local conditions dictate, such units could undertake part of the work involved in routine radiography of practitioners' cases.

May I now correct two small errors? In referring to my work, Nash, Benjamin, and Lee state that the cases investigated were seen at Hammersmith Chest Clinic. In fact the particular investigation referred to was undertaken at Willesden Chest Clinic. Furthermore, the article reference is incorrect; it should read *British Medical Journal*, 1948, **2**, 832. The *Lancet* reference given is my letter to the editor on another tuberculosis problem.—I am, etc.,

London, W.12. PETER STRADLING.

Cortisone and Tuberculosis of the Lung

SIR,—Dr. T. M. Ball (February 14, p. 404) and Mr. D. Chalmers (January 17, p. 159) inquire whether any work is being undertaken in this country on the combined use of A.C.T.H. (or cortisone), streptomycin, and P.A.S. in pulmonary tuberculosis. I described a case so treated at the Oxford Conference on Diseases of the Chest in July, 1951 (*British Medical Journal*, 1951, **2**, 296), and in November, 1952, I reported upon 10 further cases at a meeting of the British Tuberculosis Association. It is hoped that these results will shortly be published.—I am, etc.,

Harefield, Middx. L. E. HOUGHTON.

Lung Resection for Pulmonary Tuberculosis

SIR,—Dr. F. H. Young (February 7, p. 287) has given us a very valuable account of his views of the present status of lung resection for pulmonary tuberculosis based on a long and extensive experience of this disease. One is surprised, however, to read the opening statement of his paper in which he says, "In few conditions is there such a difference in the point of view of physicians and surgeons as in the treatment of pulmonary tuberculosis." With the development of fully organized services for the treatment of this disease this divergence in view must be progressively diminished, as in the conjoint conferences of sanatorium physicians, area chest physicians, and surgeons any major difference in opinion becomes ironed out by the general discussions and presentations of successes and failures. The mythical side of the treatment of pulmonary tuberculosis rapidly becomes eliminated by frank inquiry and particularly by the long-term observations of the area chest physicians, which supplement the views put forward by those who work only in the hospital or sanatorium.

The concept that Dr. Young suggests some of us in Liverpool hold, that pulmonary tuberculosis is a localized disease, has not been interpreted correctly by him. In the stage of primary invasion by the tubercle bacillus, when the lymphatic system is wide open, a bacteriaemia is usual, but in the later stages or in the stage of reinfection it is likely that the disease remains confined in most cases to the lungs. Occasionally we do see evidence of a bloodstream spread at this stage, but it is unusual. There is a general reaction of the body to this relatively localized disease, producing antibodies, white cells, etc., and cellular changes occurring in various organs due to circulation of toxins. It can be compared to a boil on the back of the neck in its general reactions, yet this is a condition which I would still call a localized disease. It is customary to state in most articles on pulmonary tuberculosis that "of

course we must never lose sight of the fact that pulmonary tuberculosis is a generalized disease." I would like a fuller explanation of this statement.

Dr. F. H. Young asks the most interesting question: "Why did the patient get the diseased area which has been removed?" He does not vouchsafe an answer to this. Does he believe that these are usually reactivation of some remnant of the primary infection? Although this not infrequently does occur, the history of most cases would suggest that exogenous reinfection is the main responsible factor.

I agree that bronchial stenosis, whether of the main bronchi or the lesser bronchi, is an important indication for resecting the affected area. Its presence can be assumed by the examination of serial radiographs in many cases, but in our experience (and we do some 300–400 bronchoscopies a year in tuberculous cases) it is relatively rare to find any evidence of permanent stenosis in the bronchoscopically visible bronchial tree. Dr. Young is most kind and complimentary to us in Liverpool on the low mortality rate of the operation of resection in our hands. I do not think the type of material varies greatly from that operated upon elsewhere, but the timing of the operation does, and this is the factor of importance. It is only by the very closest co-operation between physicians and surgeons that the timing of the operation can be accurately gauged in the best interests of the patient.

In a conjoint paper published recently (*Thorax*, 1952, 7, 310) we, both physicians and surgeons, laid down our guiding principles for submitting cases to resection, and it would be of interest to recall these: (1) Resection is undertaken of (*a*) an area which remains persistently active despite bed rest, chemotherapy, and simple relaxation therapy, and (*b*) an apparently "quiescent" area which experience indicates may reactivate with stress or intercurrent infection. (2) Resection is only undertaken when the body defences are fully mobilized. (3) The maximum localization of the disease is obtained by simple means before resection is undertaken. (4) Treatment as above usually leaves one or more areas of confluent disease and small scattered foci. The confluent areas are assessed as to likelihood of healing and resected if doubtful. The scattered small foci are unlikely to reactivate if hyperexpansion is not permitted. (5) Primary lesions only require excision if activity persists after all other forms of treatment. (6) The continued activity of a caseous pneumonia following gland rupture may require removal of that area. (7) Resection under 16 is only carried out after long activity owing to the recognized better tendency of children to heal their tubercle. (8) Between 16 and 20 the disease is unstable and resection is only carried out in these age groups on the clearest indications. (9) Hyperexpansion of remaining lung tissue must not be allowed. (10) Resection is not carried out through an area of active tuberculous endobronchitis.—I am, etc.,

Liverpool. F. RONALD EDWARDS.

Intra-arterial Injection of Thiopentone

SIR,—I read with interest Dr. J. W. Dundee's letter (February 14, p. 402). He suggests that where thiopentone has been accidentally injected into the brachial artery the correct treatment would be to induce a brachial plexus block with 1% procaine, at the same time blocking the stellate ganglion and then injecting 40 mg. of papaverine into the subclavian artery. Kinmonth[1] has pointed out that sympathetic nerve fibres are responsible for neither the initiation nor the maintenance of spasm in the large arteries and paravertebral sympathetic blocks, or such procedures as blocking the brachial plexus have no place in the treatment. I can confirm Kinmonth's observations and conclusions from personal experience.

The most effective way of treating arterial spasm is to inject a vasodilator drug (and of these papaverine appears to produce the best results) either into or around the affected artery. It is pointless to attempt to inject a vasodilator drug into the subclavian artery when the same effect can be obtained more speedily and much more easily by injecting it into the needle which is already in the brachial artery. I have not, fortunately, had the need to test the efficacy of intra-arterial injection of papaverine in order to counteract the results of thiopentone, but, in association with Dr. H. S. Pemberton, I have confirmed its almost miraculous power in relieving spasm due to other causes.—I am, etc.,

Liverpool. J. B. OLDHAM.

REFERENCE

[1] *British Medical Journal*, 1952, **1**, 59.

SIR,—Dr. J. N. Fell (January 10, p. 95) and Dr. J. W. Dundee (February 14, p. 402) both make it clear that the risks of accidental intra-arterial injection of thiopentone are ever with us.

In order to prevent the occurrence of this event, which may have serious consequences for the patient, is it not time that the teaching of the technique of venepuncture was altered? Practically every textbook where the technique is discussed recommends the use of veins in the antecubital fossa for withdrawal of blood or for intravenous injection. Your own expert in "Any Questions?" (January 10, p. 115) recommended this site for the former purpose. So long as the area on the anterior surface of the forearm is recommended as the situation of choice for venepuncture then reports of accidental intra-arterial injection will keep on occurring in the literature. I suggest, therefore, that an alternative site be used as the standard site for intravenous injection for three reasons: (1) Cohen, in a masterly paper (*Lancet*, 1948, **2**, 361 and 409), states that high division of the brachial artery occurs in one out of ten arms, and that the vasa aberrantia are found on the anterior surface of the forearm. (2) The most usual drug for anaesthetists to inject intravenously is thiopentone, and a 2.5% solution of this drug in water has a *p*H of 10.4 to 10.6 by the glass electrode method. An alkali may be injected intravenously with impunity, but not so into an artery, where the intima is particularly sensitive to solutions of high *p*H, and, in any case, the superficial aberrant arteries on the front of the forearm, like other superficial arteries, have a fuller nerve supply than deeper branches, so they are more readily thrown into spasm. (3) To perform venepuncture in the antecubital fossa the forearm must be fully supinated, the arm partly abducted, and the humerus laterally rotated. With the upper limb kept in this position so that antecubital fossa veins may be used with a Gordh-type needle for repeated injections of various drugs during anaesthesia, the risk of producing a brachial plexus palsy in addition is greatly increased. To take an unjustifiable risk is folly, and venepuncture at the bend of the elbow exposes the patient to the very real twofold risk of arterial puncture and brachial plexus palsy.

The veins on the dorsum of the hand, however, are not likely to be accompanied by arteries, and successful venepuncture here can be accomplished only with the hand flexed and fully pronated, so the risks of both arterial puncture and of brachial plexus palsy are avoided. Further, the veins here are virtually constant in position from earliest infancy onwards, and they are so large that a transfusion needle or a Gordh-type needle may be inserted into them with ease, even in very small children. Venepuncture here is no more and no less painful than it is anywhere else. The disadvantage of this site is that, on withdrawal of the hollow needle, unless firm pressure is applied over the vein *distal* to the point of puncture, blood may flow out of the puncture hole as it may in any other site. On the dorsum of the hand ecchymosis, however caused, is more noticeable to the patient and his family than at the end of the elbow, but ecchymosis is a small price to pay for freedom from the effects of arterial spasm.—I am, etc.,

London, N.W.5. JOHN HENDRIE.

Methorphinan in Anaesthesia

SIR,—In reply to the letter of Dr. R. J. Whiting (January 31, p. 271) following the publication of my paper on methorphinan as a supplement to nitrous oxide and oxygen anaesthesia (December 20, 1952, p. 1331), in my experience nausea occurs in about 5% of cases, but on one occasion only has it been prolonged or severe. I was interested to

note that Drs. J. H. Crawford and Rex Binning (January 31, p. 272) have had to administer larger dosage, but I can only confirm my previous statement that in my experience the dosage I recommended was adequate.—I am, etc.,

Dartford. A. K. BROWN.

Sensitivity to Antibiotics

SIR,—As a physician with a special interest in allergic diseases I am impressed by the increasing numbers of cases of contact sensitivity to the antibiotics occurring in the medical and nursing professions. Penicillin and streptomycin are the major offenders, mainly owing to the fact that a trained person is required for each administration. Medical practitioners are fortunate on the whole, since they are able, once their sensitivity is recognized, either to take detailed precautions when handling the material or, more simply, to delegate the injection to someone else. Nurses are in a less privileged position, and this is particularly the case with district nurses, who in the course of their domiciliary duties find that a great proportion of their work consists in giving such injections.

Symptoms are frequently mild at first, involving only the interdigital or peri-orbital areas, and may pass unrecognized for a time; but with recurring contact the condition spreads and may become very severe indeed. No satisfactory method of hyposensitization has yet been devised, and once a serious degree of sensitivity has been acquired a minimal contact with the antibiotic may produce a widespread reaction of great severity and long duration. When such a reaction has once occurred it seems unlikely that the individual will ever again be able to return to normal routine duties, and this may mean the end of a career to which many years have been devoted. The condition is not as yet regarded as an occupational hazard.

It would appear that while more and more strains of bacteria are becoming antibiotic resistant, more and more human beings are becoming antibiotic hypersensitive. In my opinion, the following precautions represent the minimal efforts which should be made to combat this tendency, which may soon reach serious proportions: (1) Rubber gloves and a face-mask with "cellophane" visor should be used while filling a syringe, giving the injection, and cleansing the syringe. (2) Syringes used for this purpose must fit perfectly and there should be no leak round the piston or at the head of the needle. (3) In hospitals or clinics where penicillin and streptomycin are largely and constantly used (chest units, V.D. clinics, etc.), or on the district, patch tests should be performed on each nurse at the time of appointment, after three months' service, and again at regular intervals of, say, three to six months. Subclinical hypersensitivity might thus be demonstrated in time to forestall the outbreak of the rash by partial or complete avoidance of contact. (4) If symptoms do develop in a nurse, the advice given to her must depend on circumstances. At probationer level she would be well advised to give up nursing entirely: if partly or fully trained, she should be guided into administrative duties or encouraged to train as a health visitor; in the case of a district nurse, the local authority should be urged to make every effort to arrange her duties so that she need never handle a syringe again. (5) The occurrence of severe clinical hypersensitivity should be regarded as an occupational hazard.—I am, etc.,

Liverpool D. BLAIR MACAULAY.

Export of Antibiotics to China

SIR,—Press reports[1] and questions[2] in the House of Commons have stated that an order placed in this country by the China National Import-Export Corporation for £500,000 worth of sulphonamides and antibiotics (including streptomycin) could not be met because export licences were not granted. We are not concerned with the effect of the embargo on British trade, but we are concerned with its effect on international medical relations. According to the Secretary for Overseas Trade[3] the export of streptomycin "is not prohibited, but it is limited to normal civil requirements," and, in answer to a later question, he stated[3]: "The permissible export by the United Kingdom to meet China's normal civilian requirements of antibiotics and sulpha drugs has been estimated by reference to our exports to China and Hong Kong of these drugs in the first six months of 1950." Direct inquiry to the Board of Trade, so we are informed, indicated that no streptomycin was exported to China or Hong Kong in that period, and it would appear, therefore, that there is a complete embargo on the export of streptomycin. In contrast, the need is immense, and it has been variously estimated that there are 30 million cases of tuberculosis in China and that the annual civil requirements may be of the order of 50 million grammes. Even in time of war many doctors have not satisfied themselves that it is proper to withhold supplies needed for the medical treatment of enemy wounded. That this country, which is not at war with the Chinese people, should deliberately withhold a drug which is recognized as a specific for certain particularly fatal forms of tuberculosis and which—in combination with sulphonamides—is the standard treatment for plague, is inexcusable.—We are, etc.,

RICHARD DOLL. DOUGLAS MCCLEAN.
D. N. LEYS. L. S. PENROSE.

London, W.11.

REFERENCES

1 *Observer*, December 14, 1952.
2 *Hansard*, column 1200, December 16, 1952.
3 Ibid. (written answers), column 300, December 19, 1952.

"Lente" Novo Insulin

SIR,—The publication by Drs. R. D. Lawrence and Wilfrid Oakley (January 31, p. 242) of a preliminary trial of lente insulin is a contribution to the ideal of one dose of one insulin per day, and it is to be hoped that the absence of a substance such as protamine or globin may allow a more uniform rate of absorption from the subcutaneous space. Hitherto a single dose of protamine zinc insulin has been satisfactory in a limited number of cases, while globin insulin given alone has been more widely useful. In 1948 I published a series of blood sugars of 21 in-patients[1] which may be compared with the lente series of 11 patients.

	Average Blood Sugars in mg.%				
	6 a.m.	8 a.m.	Noon	6 p.m.	9 p.m.
11 patients on lente insulin	128	131	168	162	167
21 ,, ,, globin ,,			151	158	

These averages are worked out from the figures given in the two papers; the variations are not great. Lawrence and Oakley (excluding case 8 on the smaller dose of lente): minimum 67 mg.%, maximum 260 mg.%. Wauchope: minimum 62 mg.%, maximum 256 mg.%.

The real test is, of course, the ambulant treatment of out-patients, for which we must wait till lente becomes available for general use. But meanwhile globin does pretty well. I have gone through the notes of 180 patients—20 young people (ages 5 to 20), 55 men (ages 21 to 65), and 105 women of the same age. They are not selected except by the accident of initial and have all been on globin insulin for at least one year since my last survey in 1948. I have excluded the large number of people over 65 who are generally stable on any insulin.

The doses of globin insulin are as follows:

	Units			
	Under 20	21 to 40	41 to 60	61 to 86
Young people aged 5 to 20		3	7	10
Men 21 to 65	21	16	15	3
Women 21 to 65	23	47	29	6
Total ..	44	66	51	19

Stability is judged by wellbeing and ability to work, constant weight, absence of insulin reactions, polyuria, or ketosis. These criteria have been maintained in the great

majority with reasonable noon blood sugars and little sugar in the morning urine tests. There are three groups where the balance is not good: (*a*) One young man and one middle-aged man who reported polyuria at night and are now taking a single dose of P.Z.I. with success. (*b*) Those who report minor insulin reactions and/or alternating bouts of thirst and polyuria. Their blood sugars vary from about 60 mg.% to about 300 mg.%. Changes to other insulins, even to two doses of soluble insulin, do not produce a lasting balance. There are two men, three women, and two children in this group. (*c*) A group of one man, six women, and two children who have been brought into hospital in a severe insulin reaction or in ketosis or coma. They have been re-stabilized, sometimes more than once, and other insulins have been tried, but they remain unstable. In all about 10% have not been really well balanced on globin insulin, and I fancy this does not differ much from the records of patients of this age on any of the present methods of insulin therapy.

These notes may serve as a yardstick to assess lente insulin when it becomes available, and it is to be hoped that the management of diabetes will become more simple and that some at least of the present "strengths" and varieties of insulin will be eliminated.—I am, etc.,

Hove. G. M. WAUCHOPE.

REFERENCE

[1] *British Medical Journal*, 1948, 2, 191.

The Catheter and the Prostate

SIR,—Is it seemly to interject among the pundits, "That depends upon the catheter"? An F.B. that fills frets the urethra. If trouble follows, do we ban the simple device or discriminate by deftly passing a loose-fitting No. 6/E Tieman catheter? For this tip—when immediate prostatectomy is imprudent—I am indebted to a general-practitioner colleague. The alternative suprapubic needle is not taboo in my department.

Mr. Arthur Jacobs (January 24, p. 217), quoting Mr. B. H. Page (December 27, 1952, p. 1415), notes that trans-urethral resection has the lowest mortality despite the use of catheters and largest-bore urethral instruments. May not the fact that the operator stops short of the anatomical line of cleavage used by the enucleating surgeon, and so avoids opening up inflammable cellular tissues in which the vasa and vesiculae are also embedded, be far more decisive than instrumentation?

Mr. J. A. Lloyd-Davies's figures (January 31, p. 257) on pre-operative infection of urine are illuminating, but they will be more cogent, and we more grateful, if he will supplement his research by tests on a similar series about a week post-operatively.—I am, etc.,

Bristol. A. WILFRID ADAMS.

SIR,—I was interested to read that Mr. J. A. Lloyd-Davies (January 31, p. 257) has found fine polythene tubing useful for temporary suprapubic drainage of the bladder in retention of urine, and I feel sure that this method is preferable to leaving a long needle in the bladder.

I would like to point out that polythene tubing can also be used successfully for continuous urethral drainage in selected cases. The open end can be closed and rounded off in the flame of a spirit lamp, and the tip can be given a suitable curve after softening in the same way. Several small holes are then cut near the end of the tube, using a razor blade. Care must be taken to avoid weakening the tubing, and the edges of the holes can be strengthened by the momentary application of the flame. Using such an improvised catheter (size 3, Allen & Hanburys), I have found it possible to keep the urine sterile for up to a fortnight, even without the use of chemotherapy or antibiotics. Urethritis is absent or minimal, and the tube does not become blocked if the urine is initially clear and infection avoided. This method has obvious advantages in the treatment of the paraplegic bladder, but it can also be applied to prostatic cases when the patient is unfit for immediate operation, and especially when transurethral prostatectomy is planned.—I am, etc.,

Liverpool. NORMAN GIBBON.

Smoking and Lung Cancer

SIR,—Professor R. D. Passey (February 14, p. 399) may be quite right that the evidence on the aetiological relation of smoking to lung cancer is not conclusive, but it would not serve the interest of the public or that of the profession if we belittle or distort the available evidence.

In view of the work that has been done on necropsy protocols covering periods up to 50 years (to mention at random only two, Steiner, P. E., *et al.*, *J. Nat. Cancer Trust*, 1950, **11**, 497, and Leschke, H., *Virchows Arch. path. Anat.*, 1952, **321**, 101), which show the *absolute* increase of cancer of the lung, the "immeasurably greater ability to diagnose and far greater opportunities for diagnosis of this condition to-day" is an argument which cannot be accepted without some reservations. I am not sure whether Professor Passey really meant his analogy of breast cancer, which might have been related to the bone and metal supports of the corsets of the Edwardian days, to be taken seriously, but, if so, I would be very glad if he would quote one work on this subject which in its scientific conception, thoroughness, and magnitude is comparable with the work carried out by the Medical Research Council on the possibility of smoking being an aetiological factor in cancer of the lung.

One could argue with Professor Passey's interpretation of the evidence on every point he mentions, but it is his final conclusion which is the most surprising, because it is a direct contradiction of the traditions and history of our profession. It would be impossible to estimate the unnecessary loss of life if, for instance, Jenner, Semmelweis, and Lister had waited to put their theories into practice until they were "sure of their evidence." As a matter of fact, as medicine is not an exact science, our responsibility as a profession always has been, and still is, a greater burden to carry than the responsibility of any other learned profession, because more often than not we have to take the most far-reaching decisions according to our conscience, on insufficient evidence, and it will always be to the everlasting credit of our profession that we have never shirked this responsibility.—I am, etc.,

Colchester FRANCIS KELLERMAN.

The College of General Practitioners

SIR,—The undersigned general practitioners met informally on January 14 to discuss the implications for Irish doctors of the report of the General Practitioner Steering Committee (*Journal*, December 20, 1952, p. 1321) and the subsequent foundation of the College of General Practitioners in London. It was unanimously agreed that these developments were of considerable importance and that a meeting representative of all general practitioners should be called in the near future in order to have the fullest discussion on the subject and to decide upon a unified line of action. Through the courtesy of the authorities of University College, Dublin, this meeting will be held in the College at 11.30 a.m. on Sunday, March 15.

This promises to be the most important meeting ever held in this country in relation to general practice. We hope that it will be attended, no matter what the personal inconvenience, not only by all those already working in this branch of medicine, whether as dispensary doctors, private practitioners, or in any other circumstances, but also by the newly qualified men and women intending to make general practice their career. It may be useful for those attending if some of the points raised at the preliminary discussion are mentioned here.

Irish practitioners have four choices in relation to the new college: (*a*) individuals having the necessary qualifications may join as members or associates; (*b*) an Irish faculty

of the new college may be formed (the method of doing this is being investigated); (*c*) an independent Irish college may be formed; or (*d*) they may do nothing.

The signatories of this letter feel that some definite step must be taken to ensure that Irish general practitioners may be enabled to secure full reciprocity with their opposite numbers in England, and that nothing should be neglected which would tend to maintain the status of the general practitioner. It is scarcely necessary to point out to readers that the field of medicine embraced by the term "general practice" has narrowed very considerably in recent years, and that many general practitioners find themselves dealing only with the clinical trivialities, while patients whom they could well treat gravitate elsewhere. In the opinion of most general practitioners there is room for great improvement in the training of medical students. While the great majority are destined to enter general practice, they are never taught, however briefly, by a general practitioner, rarely if ever see the run-of-the-mill cases which make up a general practitioner's round, and are first introduced to the general practitioner's facts of life the hard way—hard alike for the newly qualified medico and his patients.

There is no intention among the undersigned that any new group, college, or faculty formed shall be a competitor or rival of existing institutions, but rather that it shall be a co-equal partner with the object of improving the professional status of the general practitioner secondary only to the maintenance of high ethical and clinical standards in the profession as a whole. We appeal most earnestly for a full attendance of our colleagues at the meeting on March 15.—We are, etc.,

DESMOND CARNEY. J. ST. L. O'DEA.
JOHN J. MCCANN. E. A. O'REILLY.
ANDREW E. H. O'BYRNE. D. S. KEARON.
ROBERT O'MEARA. LAURENCE MASTERSON.
JOHN FLEETWOOD. J. F. O'GRADY.
NORA MCNALLY. A. RYAN.

Dublin.

SIR,—A College of General Practitioners certainly fills a gap the existence of which most of us have been too busy to notice. Other branches of medicine have their headquarters, the general practitioners had not. The usefulness of such a college must appear qualitatively and quantitatively to each of us in a different light, and it must therefore be conceded that the demand for such a college and the principles of its foundation can at the moment represent no fixed or unified opinion of general practitioners. I look upon the College's foundation with enthusiasm and pleasure, because it has a potentially important part to play in research and medical education, in both of which subjects I am deeply interested. If the prestige of general practitioners is increased by the work of the College, so much the better, but I do not put that as a reason for its foundation.

A deal of argument has arisen about the credentials necessary for a general practitioner to become a member of the College. Once a specialist or consultant has the necessary qualifications to practise his specialty, he automatically becomes a member of the Royal College of Physicians or Surgeons. Surely, then, when a doctor has obtained his qualification to practise as a general practitioner, he should become automatically a member of the College of General Practitioners? The specialist has no need to show evidence of continued good work to remain a member of his College, so why should a general practitioner? A specialist can be elected to a fellowship in the Royal College of Physicians, and a general practitioner could similarly be elected to a higher grade, if the idea is thought to be a good one. But, as I have mentioned, the general practitioner has much to contribute to medical research and education, and without a body such as a college to represent him he has little means of contribution. There are many questions which could be readily answered from the records of general practitioners. There are so many empirical forms of treatment that could easily be placed on a surer foundation. One simple example occurs in the treatment of shingles. Does liver extract help? I have not seen sufficient cases to be able to decide. A research department of the college could collect enough cases in a year to answer this question. And there are a horde of other problems, stimulating to those of us who are young enough in mind to be interested in their solution.

The education of the medical student is in the hands of specialists, and, however hard they try to give a fair share of instruction to the needs of general practice, they can for the most part act only on hearsay evidence, having no first-hand information on the subject. A College of General Practitioners can provide the needed information and take its rightful share with the other colleges in the education of the student, which is the most important problem in medicine.

I think it a point of no small moment that those groups of our profession and its ancillaries which were represented by a college or similar body—physicians, surgeons, dentists, opticians, pharmacists—came to just agreements with the Government in negotiating the new Health Service, while the general practitioners made a bad bargain from which they have had to be rescued.—I am, etc.,

Leeds. R. A. MURRAY SCOTT.

Intercourse after Syphilis

SIR,—The reply of your expert (February 7, p. 348) to Dr. T. E. Osmond's and my criticism (February 7, p. 348) of his answer to a question under the above heading would not prevent me from doing all I could to dissuade any girl—a daughter, for example—in whose welfare I was interested from marrying a man with a history of a syphilitic infection the treatment of which was completed six months or less ago. The objection that the articles by the authorities I quoted appeared before "salvarsan" was invented is beside the point. No treatment yet invented has afforded 100% success with the course prescribed at the outset before the patient is placed under observation, and, moreover, it is reasonable to believe that the more efficient the treatment, short of being completely successful, the longer is likely to be the clinically latent period before relapse is detected. Consequently, until a 100% cure has been evolved, the observation following any treatment must be longer than the longest known to have been followed by relapse. Your expert's observation respecting his failure to note any relapse more than six months after completion of treatment cuts no ice with me; it is easy to ascribe to reinfection an inconvenient (for statistical purposes) return of signs of the disease, and what American writers do in this matter does not influence me in the least. The failure of others to confirm the observations of Kertesz and of Warthin should be regarded with great caution, having regard to the experience of reliable experimental syphilographers in the difficulty of being certain that an inoculation with material suspected of containing *S. pallida* has failed. The quotation from Stokes *et al.* regarding infection of the ovum with *S. pallida* is not understood. Surely *nobody* now thinks that transmission of syphilis to the foetus is mostly by infection of the ovum?—I am, etc.,

London, N.W.10. P. A. CLEMENTS.

The Dangers of Blood Transfusion

SIR,—The letter of Dr. S. H. Waddy (February 21, p. 454) should not go unanswered. Obviously the potential donor of blood should be treated with every consideration. He should not be bled without a knowledge of his haemoglobin level, and not bled at all if it is abnormally low; his blood film should also be examined. He should be bled by a skilful bleeder, and should be regarded as one deserving the thanks of the community, which should be expressed by one of those present at the bleeding session. Further points in the care of the donor could be added. If reasonable precautions are taken, little or no harm results to him.

But even if a very occasional donor is the worse for giving blood, there is much to be set on the other side. Many lives are saved annually in the practice of obstetrics by blood transfusion, and obstetrics is but a small section of the whole field of medicine. The results in the treatment of post-partum haemorrhage have been revolutionized by

the timely use of transfusion, and the operation has contributed to improved results in placenta praevia and accidental haemorrhage. A strong case can also be made out for transfusion as one of the important measures by which the patient is made safe for surgery. It is a monstrous misuse of words to suggest that a transfusion is a "dangerous major operation."—I am, etc.,

Leeds. ANDREW M. CLAYE.

Catherine Chisholm Memorial

SIR,—Many friends and old students of the late Dr. Catherine Chisholm have expressed a wish that some tribute should be paid to her memory and that her many activities in various fields for the welfare and health of children should be commemorated. It is thought that the best way to do this will be to endow a lecture to be given annually in Manchester on some aspect of child health by a leading personality. With that object a fund has been opened to enable all those who wish to show appreciation of her great work to subscribe.

It is hoped that a worthy memorial will be forthcoming. Subscribers are asked to send their donations to the hon. treasurer, Mr. F. G. L. Whiteley, at 56, Oxford Street, Manchester.—We are, etc.,

T. F. HEYWORTH, Chairman.
SYLVIA K. GUTHRIE, Hon. Secretary.
F. G. L. WHITELEY, Hon. Treasurer.
MARY EVANS.
WILFRID GAISFORD.
A. HOLZEL.
M. L. THOMSON.
NESTA H. WELLS.

Manchester.

POINTS FROM LETTERS

College of General Practitioners

Dr. H. H. LEESON (Worthing) writes: With general practice as it is, there is nothing to distinguish the good clinician from the bad. Certainly the size of a man's list is no criterion. Should not there be some goal or reward which the good doctor could try to obtain, some degree, or diploma, or certificate of merit, with consequent financial benefit, marking out those whose keenness and good work deserves recognition? Is it then surprising that so many young men grasp with eager hands any suggestion or plan which will lift general practice of the future out of the rut into which it has so largely fallen? The college has education and training for general practitioners well in mind, and if through its influence it can do something to introduce more general-practitioner-mindedness to students in their clinical years instead of the almost entirely specialist outlook which comes from their present teachers, and if it can encourage the teaching of clinical medicine in the wards of the municipal hospitals, where the "flotsam and jetsam" of medical practice abounds, instead of the rather hothouse atmosphere of the teaching hospitals, many present-day students would have cause to bless the college.

Home Nursing and First-aid Lessons

Dr. MARY AINSCOW (Penrith) writes: Dr. W. S. Parker (February 7, p. 337) may be interested to know that for many years the St. John Ambulance Brigade has been conducting classes for girls and boys aged 11–16 in first-aid and home nursing. Wherever these classes have been held the general practitioner, the district nurse, and the public have praised their usefulness. Also, they have been the means of guiding many young folk into the nursing profession.

Dr. WINNIEFRED M. GRAY (Aberdeen) writes: It is some years now since I first made a suggestion that the subjects mentioned in Dr. W. S. Parker's letter (February 7, p. 337) should be included in the school curriculum. Such teaching is very much needed, and the course should be for both boys and girls. All children should have passed their first-aid examination before they leave school. The girls should have a course of sick nursing and the boys be taught stretcher drill and fire-fighting. For several years now I have been giving lectures on first aid, and of the 90 enrolments for my first-aid classes last winter at least a third would have benefited more from a course of domestic emergencies and sick nursing than from the existing course, which caters more for members of the regular ambulance service and the Civil Defence workers. It is a waste of public money and not safe for the community to rush people of all ages through a course of ten lectures (fewer even is suggested under Civil Defence) and let them loose on the public. Teaching of such subjects efficiently during school life would give the country a band of workers ready to cope with accidents and sickness in the home, in public places, and during travel emergencies.

Damages Against Casualty Officer

Mr. W. D. PARK (Shenfield, Essex) writes: May I add my expression of dismay at the recent case in which damages were awarded against a casualty officer (January 17, p. 166)? . . . I would suggest a change regarding medical witnesses, so that, instead of being called by one side or the other, a board of medical experts should be available to express accepted medical opinion. Such a board could be composed of representatives of the Royal Colleges, universities, and other suitable bodies. Finally, may I express the hope that this judgment will be reversed on appeal?

Dr. L. A. GIBBONS (Reigate) writes: I was glad to see (February 7, p. 331) that many other doctors are conscious of the unfairness to the casualty officer; but the implications are very widespread. . . . Under the present decision in this case (1) no casualty officer can take responsibility, and consultants will have to see every patient, (2) if any doctor, after careful examination, makes a misdiagnosis he is liable to have damages awarded against him—a most untenable position—and (3) the hospitals will not be held jointly responsible with their medical officers—also an absurd position. I sincerely hope that other members of Council will take this matter up to demonstrate that the British Medical Association is concerned with the affairs of each and every doctor.

Kindness to Patients

Mr. K. W. MONSARRAT (Faringdon, Berks) writes: I wish to endorse the comment you make (January 31, p. 264) on the report of the Central Health Services Council, that "if there are many hospitals which need to be given these elementary instructions it is surprising that the reputation of the hospital service stands as high as it does with the public." I think, moreover, that the attention of the profession should be drawn to the version of this report given by *The Times* in a summary and leading article on January 26. There can be no question that this summary and leader convey to the reader that humane sympathy with the patient has, up to the present, been far from characteristic of British hospitals in general. It has been said from time to time that it is a British habit to run down ("denigrate" is, I believe, the new word) British institutions and customs. It seems to me incredible, however, that any body of medical men with hospital experience would lend itself to doing this in the case of the British hospital its members have known. Having obtained and read a copy of the council's report, it is a relief to say that this accusation cannot be brought against it. One criticism that can be fairly made is that the report fails to make any general acknowledgment of the humanity and benevolence which have characterized the treatment of the patient in the hospitals of this country for many years past.

Metal Filings in Tinned Food

Dr. K. P. DURKACZ (Edinburgh) writes: The "tin of soup" opening habit is widespread. In the process of tin opening a lot of metal chips or filings fall and mix with the contents. Consequently a considerable amount of metal particles must thus be consumed. In order to bring out this point with more force I would urge you to perform the following experiment. Take an empty tin, thoroughly dried, and cut the already open end with a pair of shears, so that no ledge is left. Place the tin, open end down, on a flat surface covered with a sheet of white paper. Without moving, open the tin in the usual manner. It may come as a major revelation to find on the table a considerable amount of metal particles after the tin is lifted. . . . The amount of filings and their size depend on the method of opening. They will be shown more clearly when collected on the tip of a magnetized penknife. I do not intend to comment on what happens to these filings when they fall into the soup or what their effect may be on the alimentary canal.

Oesophagitis

Dr. G. S. ASTON (Torrington) writes: Recently attention has been focused on regurgitation of gastric contents into the oesophagus causing a condition called oesophagitis. This, I have noticed, tends to be more common in men, particularly of the 50 age group and usually in the heavier types. A good pointer to this can be found if the pain or discomfort occurs in the evening after a fairly substantial meal. It can be easily elicited by pressure sustained on the upper abdomen for a few minutes with the patient lounging in a chair. This is really what happens to most men in a comfortable club type chair, hence the pain.

Obituary

MARC DANIELS, M.D., M.R.C.P., D.P.H.

Dr. Marc Daniels, a member of the Medical Research Council's scientific staff, in its Tuberculosis Research Unit, died in Westminster Hospital on March 3 after an illness borne with great courage. In the first rank of research workers in human tuberculosis, his reputation was steadily increasing, both here and abroad. He was 46 years of age.

Educated at Manchester Grammar School and University, where he took a B.Sc., Daniels was intended for a career in textiles; but after a short experience of commerce he decided that his interests lay in medicine. He qualified M.D. in Paris in 1936, worked in a French tuberculosis sanatorium, and in 1937, at the age of 30, took the Scottish Triple Conjoint. The next two years were occupied by a house post in Hereford, experience in the North-Western Fever Hospital, and in working for the London University Diploma in Public Health. He was then for two years assistant medical officer of health and tuberculosis officer in Lincolnshire (Kesteven), where his preference for group to individual medicine became established. This statistical approach, combined with a growing interest in research, led, by a chance trail, to his appointment in 1942 as the third in a line of Scholars to the Prophit Tuberculosis Survey, Royal College of Physicians. He held this post until 1945, the work culminating in the important Prophit report on *Tuberculosis in Young Adults*, in the preparation of which Daniels himself played a major part. This report threw new light on the epidemiology of tuberculosis in young persons exposed to special contact risks, particularly nurses, and led to practical improvements in tuberculosis control among hospital staff. In this connexion, too, Daniels gave valuable assistance in the official deliberations that resulted in 1951 in the inclusion of tuberculosis in nurses as an industrial disease.

In 1945 the appalling post-war incidence of tuberculosis in Europe led Daniels to join the staff of Unrra, and he spent nearly two years as a tuberculosis consultant in Italy, Poland, Czechoslovakia, Austria, and Germany. Some of his observations were presented in his Milroy Lectures on "Tuberculosis in Post-War Europe," given to the Royal College of Physicians in 1949. He had become a Member of the College in 1948.

In 1946 streptomycin was introduced into this country as the first agent to show real promise in the treatment of tuberculosis. With memories of past false hopes raised for gold and other remedies on the basis of subjective impressions of small series of mixed cases, it was essential to assess precisely and rapidly the real value of the antibiotic. The Medical Research Council promptly set up a special committee, under the chairmanship of Dr. (now Sir) Geoffrey Marshall, and Daniels was invited to take charge of the practical co-ordination of its controlled clinical trials. He joined the group that later became the Council's Tuberculosis Research Unit and threw himself into the work with characteristic zest. It suited him admirably; and with the collaboration of Professor Bradford Hill in the statistical design of the trials, and the wholehearted co-operation of clinicians and laboratory workers up and down the country, he ensured the success of this the first strictly controlled clinical investigation in tuberculosis. Further trials followed, and the Committee's reports, prepared for it by Daniels, rolled forth: on "Streptomycin Treatment of Pulmonary Tuberculosis" (1948), "Streptomycin Treatment of Tuberculous Meningitis" (1948), "Treatment of Pulmonary Tuberculosis with Streptomycin and P.A.S." (1950), "Prevention of Streptomycin Resistance by Combined Chemotherapy" (1952). Collating data from each of these, he published in 1952 a personal paper in collaboration with Professor Bradford Hill ("Chemotherapy of Pulmonary Tuberculosis in Young Adults"). This series of trials, many of them published in the *British Medical Journal*, attracted world-wide attention, and the results were generally accepted as providing a sound basis for clinical chemotherapeutic management. More than this, the methods developed constituted an advance in the evaluation of new drugs, not only in tuberculosis but also in other acute and chronic diseases. Daniels was invited to lecture and advise in France, Scandinavia, the U.S.A., and elsewhere, and the methodology of the trials was codified in his paper in the *British Medical Bulletin* (1951) and in his contribution to the Colloquium on the Chemotherapy of Tuberculosis held by the M.R.C. of Ireland in 1951. He was a member of the Streptomycin Subcommittee of the World Health Organization's Expert Committee on Tuberculosis. In the last year of his life he was mainly occupied with the M.R.C.'s trials of isoniazid, and to him goes the major credit for the speed and efficiency with which they were initiated and sustained, under a new design requiring monthly reports for each patient and a continual analysis of the data. As a result, a first report, "Treatment of Pulmonary Tuberculosis with Isoniazid," could be published no more than six months from the start; a second report appears in our opening pages this week. With the more recent stages of this work he maintained a close contact and intense interest in spite of his illness, giving helpful criticism to the junior colleague upon whom, in his absence, its main brunt fell.

Daniels was secretary of the M.R.C.'s Tuberculin Survey Committee and of its Tuberculosis Vaccines Clinical Trials Committee. Under the former, he analysed the results of a national survey of tuberculin sensitivity at various ages based on 95,000 children and young people in England and Wales, and prepared the report (1952); under the latter committee, he was from 1950 onwards taking the main responsibility for developing and co-ordinating the current large-scale trials of B.C.G. and Vole bacillus vaccines among over 50,000 school-leavers in the Home Counties and the Birmingham and Manchester areas.

Daniels was frequently called upon by other bodies for his knowledge of epidemiology and tuberculosis control. In 1947, with Dr. D'Arcy Hart, he visited the British Zone of Germany and Berlin at the request of the Foreign Office, to investigate the prevalence of tuberculosis, which was alleged to be rising rapidly. Their report (1948) concluded that these fears were unfounded, and were due largely to the sad state of German morbidity statistics; they gave an optimistic forecast of the tuberculosis trends, which has since proved correct. In 1951 and 1952 he investigated the tuberculosis situation in displaced persons' camps in Trieste, on behalf of the U.N. High Commissioner for Refugees and W.H.O., and recommended improvements. He visited Poland and Yugoslavia for the British Council.

Into the short 15 years of his medical career, Daniels thus crowded a host of valuable activities. He worked with tremendous intensity, coupled with strict accuracy—"ruthless objectivity" a colleague once described it. A somewhat spartan approach to life helped him in many situations, not least in his illness. His enthusiasm extended beyond his work; he was a discriminating critic of painting and the theatre, and himself acted, photographed, and modelled with skill, and even took up the flute. He was not easy to get to know intimately, but those who did recognized his charm and warmth and the variety of his interests. Children were attracted to him and he loved their company. Daniels had been a sincere socialist for many years, and his abhorrence of the effects of war led him to join the Medical Association for the Prevention of War. He married, first, Anne Burgess in 1940, and there are two daughters, aged 8 and 11; in 1949 he married Kay Graw, who had been a fellow-worker in Unrra.

We are indebted to Professor A. BRADFORD HILL for the following appreciation: In a leading article, published in the *British Medical Journal* nearly five years ago, commenting upon the Medical Research Council's first controlled trial of streptomycin in pulmonary tuberculosis, it was suggested that the plan then adopted "may well serve as a model in this field." The prediction was right. Many therapeutic trials, not only in the field of tuberculosis, have been founded upon this early essay, and much of the credit for its success must go to Marc Daniels. I came to know him well at this time, and through his shy and diffident manner there stood out very clearly the characteristics that led to that success—an urge for perfection and accuracy, a patience and capacity for hard work that enabled him to seek that perfection in every detail, and an intellectual honesty that made him interested in nothing but gaining the truth. To this he added an organizing ability which kept the trial running smoothly in many different centres. It was the ideal combination of characteristics. He had also, I found later as we continued to work together, a very large share of that statistical "common sense" which is anything but common, and an outlook upon the ethical problem which made him pause and reflect at every step in a controlled trial. With all his eagerness for the experimental approach, no one could have been more humane than Daniels, more careful of the patient's well-being. He never resented criticism; he would argue the point quietly but effectively, and if he concluded he was wrong he would cheerfully start his project or the writing of a report all over again. He wrote concisely and dryly, in keeping with his character. He was too self-effacing and retiring ever to talk about himself, and so was a difficult person to get to know well. Indeed, after five years of friendship I knew practically nothing of his life. Yet his honesty of purpose was so apparent as to command one's admiration—as indeed did his courage in these last weeks—while his quiet shy smile and constant friendliness in discussion inevitably drew one's warm regard and affection. His death at an early age is a serious loss to British experimental medicine.

Sir LOUIS GREIG, K.B.E., C.V.O., M.B., Ch.B.

A friend of royalty and of other high personages, Group Captain Sir Louis Greig died at his home at Richmond Park on March 1 at the age of 72. He underwent a serious operation last December, and had recovered from its effects sufficiently to be able to spend Christmas at home with his family, but he recently suffered a relapse.

Louis Leisler Greig was born on November 17, 1880, the son of Mr. David Greig, of Glasgow and Fife, and was educated at Merchiston Castle School, Edinburgh, and at the University of Glasgow, where he graduated M.B., Ch.B. in 1905. Entering the Royal Navy as a surgeon lieutenant in the following year, he saw service in H.M.S. *Hibernia* and *Cumberland*, and at the Royal Naval College, Osborne, and the Royal Marines Depot, Deal. It was while at Osborne that he first met Prince Albert, later King George VI, and thus began a friendship which was ended only by the death of His Majesty last year. After Prince Albert's serious illness in 1917 Greig did much to restore him to health, and by example and encouragement he played his part in moulding the Prince's character.

Greig was serving with the Royal Marines Brigade when he was taken prisoner by the Germans in October, 1914, but, under the arrangement for the exchange of naval prisoners of war, he was repatriated in September, 1915, in time to witness the Battle of Jutland from the crow's nest of Jellicoe's flagship. In April, 1918, he transferred to the Royal Air Force with the rank of major, later becoming group captain. After the war Greig was Comptroller to the Duke of York, as Prince Albert had now become, from 1920 to 1923, and he was Gentleman Usher in Ordinary to King George V from 1924 to 1936 and Extra Gentleman Usher to King George VI from 1937 until His Majesty's death. Greig's services to royalty were recognized by his appointment as C.V.O. in 1917, and he was created K.B.E. in 1932, in which year he was appointed Deputy Ranger of Richmond Park. The recipient of a number of foreign honours, Greig was a Chevalier of the Légion d'Honneur and of the Ordre de Couronne of Belgium, and he was awarded the Belgian Croix de Guerre, the Dutch Order of Orange-Nassau with Swords, and the Legion of Merit of the U.S.A. In the last war he served as personal air secretary to the Secretary for Air from 1940 to 1946. He was appointed a Deputy Lieutenant for London in 1948.

As a young man Greig played Rugby football for Scotland, and was captain of the national fifteen several times. He was also a tennis enthusiast, and played the game often with the late King. In 1920 they won the men's doubles in the R.A.F. championships, and six years later they appeared together in the doubles at Wimbledon in the All-England championships. On that occasion, however, they were eliminated in the first round, but history was made, for it was the first time that a member of the Royal family had appeared in the championships. Greig was chairman of the All-England Club and of the Not-Forgotten Association; he was also a governor of Westminster Hospital and formerly of Guy's. He married Phyllis, daughter of Mr. J. Walter Scrimgeour, and had one son and two daughters.

HAROLD BALME, O.B.E., M.D., F.R.C.S.

Mr. H. W. S. WRIGHT contributes the following memoir of Dr. Balme, whose death we recorded in these columns last week:

The death of Harold Balme will leave a void, not only among his more intimate friends, but in the minds of doctors and students and medical administrators in widely separated parts of the world. When he had obtained the F.R.C.S. and D.P.H. he went to China as a missionary, and worked for some years in the interior at Tai Yuan Fu, where among other things he learnt something of the educational needs of provincial China. Later he went to Tsinanfu, the capital of Shantung, where he played a distinguished and critically important part in building up a modern medical school, starting with the building of a large, well-designed mission

hospital. This subsequently became a part of a university with faculties of arts, theology, and medicine. Its degrees were recognized by McGill University, and were registered in Canada. Balme was first professor of surgery and dean of the medical school, and then president of the university. It was at one time a centre for a research project of the Royal Society on the transmission of kala-azar, and it had a translation bureau which was partly responsible for the translation of standard textbooks into Chinese and the publication of a Chinese medical journal. Harold Balme's major contribution to this not inconsiderable achievement was his insistence that scientific education in China should not under any circumstances be used to produce half-educated medical assistants and teachers for mission hospitals and schools, but that their standards should be comparable with those of western universities. Further, his experience had shown him that at least one of the four universities should teach in Chinese. These rather obvious ideas were at the time the subject of acute and sometimes acrimonious controversy.

With Harold Balme, once a notion had been clarified it was never left to fade gently away and disperse with the tobacco smoke which had attended its birth. He persuaded mission boards and the Rockefeller Foundation to make it live in bricks, mortar, and personnel. To teach science, a method born of the Greek way of thinking, in a language adapted to expressing a very different set of ideas to very different cultural values, is in itself a formidable task. People who knew their subjects well enough and who were prepared to learn Chinese, adapting it to their needs as they went along, were not easy to find. Still, it was done, and in the years that followed this co-operative effort made a useful contribution to educational progress in North China. If for the medical side of it credit should go to some more than others, Samuel Cochrane, Harold Balme, and Roger Green of the China Medical Board deserve it.

About 1927 Balme felt that he had to go home, and went into general practice in Kent. Not having done any medicine for about 10 years, he proceeded to the degree of M.D., a feat which he regarded as merely a question of organization easily dealt with. It was the best and most successful general practice I have known. Every case had notes which would not have disgraced any hospital. He was not a born clinician and never became a remarkable one, but he knew how to find out what was the matter with people and how to organize their recovery. It is characteristic of him that during this period he wrote a book on pain related to its treatment in general practice. This practice he had to abandon on account of a long and trying illness which brought with it some disability.

After his work in the E.M.S. during the war, his major interest was rehabilitation, which he regarded more as an attitude of mind than as an affair of gymnastics, important as the latter are. He organized the Ministry of Health branch of rehabilitation and was their consultant adviser till 1951. He was also director of the welfare services of the British Red Cross Society, and as such he travelled widely all over Europe, advising on rehabilitation centres. In 1950 Balme's work on rehabilitation was enlarged by his appointment as adviser to the United Nations and World Health Organization, and also to the World Veterans Federation. This wide field took him on many laborious journeys to the United States, Egypt, and all over Europe. The setting up of international plans and action for the relief of all kinds of disability owed much to his contributions. Treatment for handicapped children was his special concern. In the last year of his life, although he was in constant pain, he organized study courses for experts from war-devastated countries, and he accomplished his final journey in Sweden, Finland, and Denmark last autumn, and was able to see his work successfully concluded.

Many of the last years of his life were a weary tale of suffering serenely borne. He was unable to survive an extensive operation, and he died on February 13, leaving behind him a widow, two sons, and two married daughters. They assuredly have the vivid and understanding sympathy of many friends. His life, whether as a missionary or as an administrator, developed a consistently clear behaviour pattern. He early realized that creative ideas, of whatever kind, be they religious or secular, have in themselves a dynamic of their own, and his task, as he conceived it, was to crystallize them out in terms both of functioning institutions and human endeavour. This was his ideal, and in its practice he was supremely successful.

We are indebted to Dr. JOHN D. KERSHAW for the following appreciation:

As chief of the rehabilitation unit in the United Nations Secretariat in 1951–2 I was one of Dr. Harold Balme's closest professional colleagues in the last phase of his work, and I feel that some fuller comment upon it should be made in his obituary notices. He joined U.N. as a consultant at an age when most men are retiring from active professional work. U.N. and its Specialized Agencies had all been finding themselves engaged on problems of rehabilitation of the handicapped, and it was necessary to integrate their separate activities into a co-ordinated whole. As chairman of the joint working party of U.N. and the Agencies, Balme's special qualities of experience and personality made him the perfect catalyst, and the great measure of unity which was achieved between 1950 and 1952 was largely due to him. In the more active task of expert adviser to some of the less highly developed countries he combined a realistic outlook with unbounded enthusiasm, and several U.N. projects which are now in operation owe much of their success to him.

The work was exacting and probably hastened his death, but he never spared himself. Even those working with him did not always realize that he sometimes came straight to the conference table from a sick-bed to which he would return as soon as the meeting adjourned. I have, at his request, taken difficult problems to him in a hospital ward and found him as alert and helpful as if he were well and in his office. The Report on a Co-ordinated International Programme for the Rehabilitation of the Handicapped, which was presented to the U.N. Social Commission last year, and which is likely to form the basis of future developments in this field, was largely Balme's work, and in its fulfilment he will have a fitting memorial.

A. H. NORRIS, C.B.E., *M.C.*, M.R.C.S.

Dr. Arthur Herbert Norris, C.B.E., *M.C.*, who was chief inspector of the Children's Branch of the Home Office from 1918 until his retirement in 1940, died at Dawlish, Devon, on February 20 at the age of 77. The son of the late Rev. C. E. Norris, vicar of Falings, Rochdale, he was born in 1875 and educated at Ellesmere, Shropshire, Manchester University, and St. Thomas's Hospital, where he qualified in 1906. He obtained the D.P.H.(Vict.) in 1910 and the special certificate in school hygiene the following year. At Manchester he held a number of appointments, including senior medical officer of the Manchester Children's Dispensary. He was an assistant medical officer of health and school medical officer of the Berkshire County Council for some years, and shortly before the outbreak of the first world war he was appointed to the post of medical inspector of the Children's Branch of the Home Office. When war broke out he was called to the colours and served overseas as a battalion medical officer of the Manchester Regiment, being awarded the Military Cross. He was demobilized in 1917 to enable him to return to his post at the Home Office at a time when the health of the children in the industrial and reformatory schools was causing serious concern. In the same year he was appointed chief inspector of the Children's Branch in succession to Charles Russell, and his influence was rapidly felt. He served in 1927 on the departmental committee on the Treatment of Young Offenders, which culminated in the Children and Young Persons Act of 1933. In 1931 he was honoured with the C.B.E. Dr. Norris had a dynamic and genial personality, a remarkable memory, and an original mind. He did much to humanize the regime of the industrial and reformatory

schools, which in 1933 became known as approved schools. He had a clear insight into the care and education of children and young persons, and through his guidance vocational training to a large extent replaced tasks of no educational value in approved schools. After his retirement he maintained an active interest in the care of children, and was for a time adviser to the National Children's Home, and served as a co-opted member of the Children's Committee of the Devon County Council. For many years he was a manager of a number of approved schools in the West Country. By his inspiring leadership Dr. Norris brought out the best in those who worked under his direction, infusing them with his enthusiasm and humanity. He will be missed by his friends and former colleagues of the Home Office.—A. P. R.

By the death of Dr. JOHN MORGAN, of Rock Ferry, on February 15 at the age of 51, Birkenhead has suffered a sad loss. John Morgan was born at Tregaron, Cardiganshire, on October 30, 1901, and he received his medical education at the University of Liverpool, graduating M.B., Ch.B. in 1926. After gaining experience as an assistant, he joined a partnership at Rock Ferry, Cheshire, in 1929, and, despite the disability of asthma, from which he was a lifelong sufferer, he built up a large practice which, as the result of his kindly disposition and constant attention to work, made heavy demands on his health. During the last war he was in charge of a large first-aid post, and his readiness to be of assistance at any time won for him the respect and admiration of everyone in the district. The war years took heavy toll of his strength, but, in spite of the fact that he was often more ill than some of his patients, no call for his help, night or day, was left unanswered. He also served as a member of the Birkenhead Local Medical Committee. The crowds at his funeral service showed how Dr. Morgan, through his kindliness, had achieved greatness. To his widow and their three young children our deepest sympathy is given, for he was devoted to them.—H. C. W. B.

Medical Notes in Parliament

Joint Ministry of Pensions and Insurance

Notice of the Government's intention to combine the Ministry of Pensions and the Ministry of National Insurance in one department was given to the House of Commons on February 26 by the Prime Minister. In the course of his statement Mr. WINSTON CHURCHILL said it was the Government's policy to make, as opportunity afforded, such changes in the organization of Government departments as would simplify administration and reduce costs.

It was proposed to amalgamate the Ministry of Pensions with the Ministry of National Insurance as regards the award and payment of war pensions and allowances. The new Ministry would be known as the Ministry of Pensions and National Insurance. The medical treatment undertaken by the Ministry of Pensions (including the management of hospitals and the supply of artificial limbs, surgical appliances, and invalid vehicles) would be transferred in England and Wales to the Ministry of Health, and in Scotland to the Department of Health for Scotland.

Mr. Churchill assured the House that the greatest care would be taken to ensure that war pensioners and their dependants were not in any way adversely affected by these changes. An additional Parliamentary Secretary would be appointed to the new Ministry to look after their pensions and allowances. The Central Advisory Committee on war pensions would continue to function. Arrangements would be made, in consultation with the Government of Northern Ireland, to meet the requirements of war pensioners resident in Northern Ireland. The changes would not take place before the summer recess, and an explanatory White Paper would be issued before the matter was debated.

Prescription Charges

Mr. A. BLENKINSOP asked the Minister of Health on February 26 what financial saving he now estimated would result from the charge for prescriptions, how much of this saving would result from a fall in the number and cost of prescriptions, and how the savings compared with the estimate given at the time of the introduction of the Health Service Act, 1952.

Mr. IAIN MACLEOD replied that the estimated amount of the prescription charges paid or to be paid in 1952–3 by patients in England and Wales was about £5m. The number of prescriptions dispensed during the year was not now expected to be less than in 1951–2. This was due to the recent fogs and the influenza epidemic. The average cost per prescription was this year continuing the upward trend of previous years. On the assumption that the charges would operate for a full year and that the number of prescriptions dispensed in 1952–3 would be 10% less than in 1951–2, it was originally estimated that patients' payments in 1952–3 would amount to £6.8m., and that the further saving due to a reduction in the number of prescriptions would be £3.9m.

Air Pollution

Mr. ELLIS SMITH asked the Minister of Housing and Local Government on February 24 if he would have an investigation made into the amount and effects of air pollution over Stoke-on-Trent, Manchester, and Stockport, with a view to the preparation of a report, such as that on air pollution in Donora, Pa., U.S.A.

Mr. A. E. MARPLES, the Parliamentary Secretary, stated that systematic measurements of atmospheric pollution were already being made in these and other towns, and investigations into certain factors were in progress. The results of the Donora report had been studied and were being borne in mind.

Bread Improvers

Mr. BERESFORD CRADDOCK asked the Minister of Food on February 25 what further details he could give of the investigations into bread improvers. Major LLOYD GEORGE replied that the investigations were being undertaken by the Ministry of Health, the Medical Research Council, and the research associations of the milling and baking industries in association with his department. They were designed to assess the relative suitability of various bread improvers, including agene, chlorine dioxide (which was widely used in the United States), vitamin C, and a recently developed aeration process in which improvement was affected by high-speed mixing. The problems were complex, and a quick answer could not be anticipated.

Tetanus Infection

Dr. BARNET STROSS asked the Minister of Fuel and Power on February 23 whether he would state the precautions contemplated for the protection of men who work in an environment where the risk of infection by tetanus after injury was present. Mr. GEOFFREY LLOYD stated that the small number of fatal cases of tetanus among miners, not more than one or two per year, suggested that the first-aid treatment of injuries at mines had provided reasonably effective protection against infection with the disease. Recently, however, the National Coal Board gave instructions that when a man was injured at a colliery where the risk of infection with tetanus was likely to be present, and was sent to hospital, the staff of the colliery medical or first-aid room must notify the hospital accordingly.

Private Members' Bills

The Pharmacy Bill was given a second reading in the House of Commons on February 27, after a brief debate. Its main purposes are to combine the two existing registers of chemists and druggists into one register of pharmaceutical

chemists, and to give effect to proposals for improved standards for qualification and registration. It also removes the disqualification on members of the medical profession being registered as pharmaceutical chemists. It was moved by Mr. JOHN HALL, and supported by Mr. SOMERVILLE HASTINGS and Mr. HUGH LINSTEAD. The second reading was agreed to.

The Abortion Bill came up for second reading in the closing minutes of the sitting on February 27, and was "talked out." Its sponsor, Mr. J. REEVES, was still speaking when the sitting came to an automatic close at 4 p.m.

The debate was due to be resumed on March 6.

Medico-Legal

SELLY OAK FINDINGS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On February 19 the committee appointed by the Birmingham Regional Hospital Board to inquire into allegations of bad doctoring and bad nursing at Selly Oak Hospital[1] made its report and concluded that the allegations by Professor J. M. Webster of bad nursing and bad doctoring were not borne out.

The committee attributed the fracture of Mrs. L. Greaves's femur to the falling or turning over of her paralysed leg as she was being put to bed, without any failure of the three members of the staff who were lifting her. As to the constipation, the committee found that after Mrs. Greaves had been removed to the surgical ward there was no reason for Sister I. Harkin to suspect constipation, in view of what she herself saw, the reports that she was given, and the patient's fluid diet. It was satisfied that there was no lack of proper care and skill.

The allegations of bad doctoring fell under four heads. Dr. Troughton and Dr W. M. Philip could in no way be blamed in connexion with the constipation. In the light of their finding that there was no bad nursing in the treatment of Mrs. Greaves's bowels, the committee held that no blame could attach to Dr. K. Harrison for failure to know she was constipated before the swelling in her abdomen was found. It was satisfied that Dr. Harrison was justified in not diagnosing this as due to impacted faeces.

It thought that Dr. Philip, Mr. G. R. Clarke, and Dr. Harrison were justified in taking no steps to deal with ascending genito-urinary infection. Though this was a condition likely to develop, the usual signs of high temperature and rigors were entirely absent, and these matters were properly regarded as secondary to the fracture treatment and to the comfort of the patient.

The committee accepted Dr. Harrison's explanation that he had not reported his diagnosis of the lump in the abdomen as a tumour to Mr. Clarke because he did not consider it to be urgent, and was satisfied that, even had it been reported and had impacted faeces been diagnosed, nothing could have been done which would not probably have done more harm than good.

The complaint that Dr. Harrison had failed to have the urine obtained by catheter from Mrs. Greaves analysed when he saw that it was dark, rather thick, and offensive had not been pursued at the inquiry by Professor Webster. Although the committee would have expected that the practice would be to make a routine ward test, they accepted that this would have served no useful purpose having regard to the fact that Mrs. Greaves was very ill and that the view of all the experts except Professor Webster was that, apart from making her and her fracture as comfortable as possible, nothing could be done to improve her condition. In all four respects, therefore, the committee decided that the complaints of bad doctoring were not made out.

[1] *British Medical Journal*, February 7, p. 341.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 14** (No. 6) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire
Diphtheria	24	1	13	0	2	34	4	15	0	0
Dysentery	320	36	113	16	1	592	82	40	0	2
Encephalitis, acute	4	0	0	1		3	1	0	0	
Enteric fever:										
Typhoid	4	0	0	0	1	2	0	1	1	4
Paratyphoid	6	0	1 (B)	0	0	6	0	0	0	1 (B)
Food-poisoning	40	6		0		89	14		0	
Infective enteritis or diarrhoea under 2 years				12	14				13	12
Measles*	32,359	1507	372	76	293	4,425	65	456	136	97
Meningococcal infection	53	2	19	2	3	49	4	11	0	3
Ophthalmia neonatorum	28	2	7	0		35	6	7	0	
Pneumonia†	2,431	228	306	33	10	1,105	41	340	11	1
Poliomyelitis, acute:										
Paralytic	15	2	0	1	4	11	1	3	2	2
Non-paralytic	1	0				6	0			
Puerperal fever§	294	33	18	1		216	37	9	6	
Scarlet fever	1,515	61	247	34	82	1,416	114	207	26	36
Tuberculosis:										
Respiratory			170	25				134	26	
Non-respiratory			29	3				26	0	
Whooping-cough	2,238	96	196	34	116	2,686	91	306	100	72

DEATHS in Great Towns	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire
Diphtheria	0	0	0	0	0	0	0		0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	8	2	3	4	1	18		5	0	0
Influenza	530	111	3	3	3	40	9		2	0
Measles		0	0	0	0		0		0	0
Meningococcal infection		1	2				1			
Pneumonia	802	158	22	12	11	354	64		13	16
Poliomyelitis, acute	2	0			0	2	0			0
Scarlet fever		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory	184	35	18	6	10	181	20	25	3	9
Non-respiratory		4	0	0	2		2	2	0	3
Whooping-cough	6	2	0	0	2	2	0		0	1
Deaths 0–1 year	293	37	31	11	24	285	28	41	8	20
Deaths (excluding stillbirths)	9,102	1579	644	111	199	6,759	988	829	155	219
LIVE BIRTHS	6,926	1045	880	155	364	7,680	1155	914	209	410
STILLBIRTHS	181	28	19			191	29	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

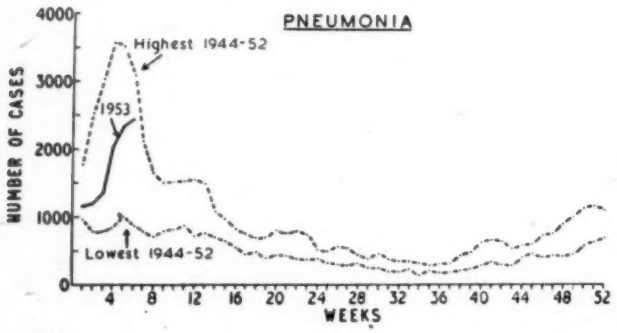
Vital Statistics

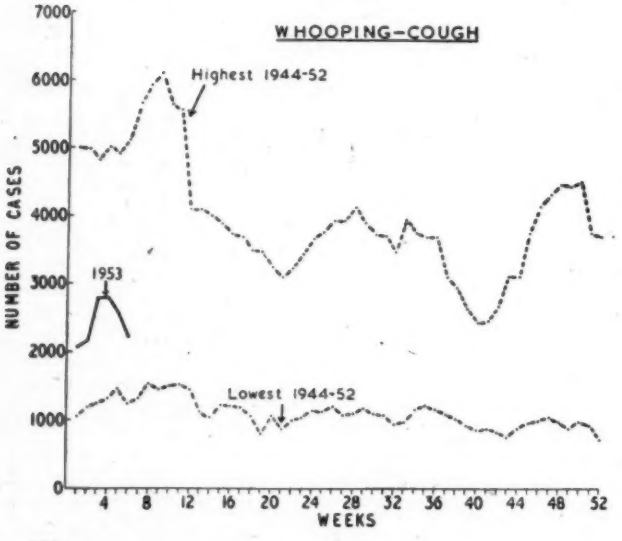
Influenza

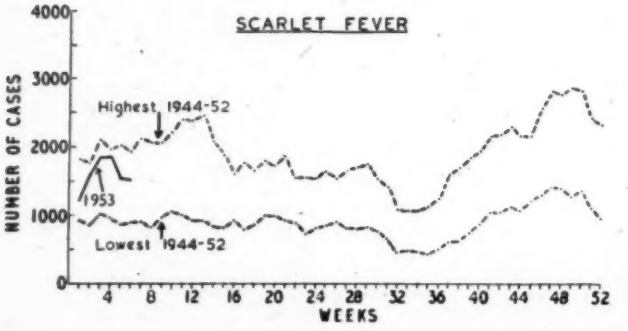
In the week ending February 21 there were 521 deaths from influenza in the great towns of England and Wales. This is nine fewer than in the previous week, and is the first week this year to show a decline in the number of deaths. The fall was particularly noticeable in London and the south-east, while in each of the regions in the north of the country there was a slight increase over last week's figures. The outbreak in the southern part of the country is thought to be subsiding gradually rather than abruptly.

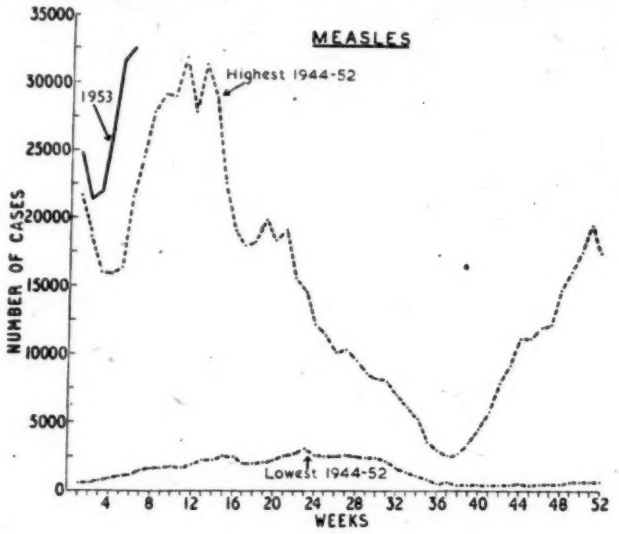
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The only large variations in the trends of infectious diseases in England and Wales during the week ending February 14 were a rise of 865 for measles, from 31,494 to 32,359, and a fall of 333 for whooping-cough, from 2,571 to 2,238.

The number of notifications of measles was the largest ever recorded, and was 502 more than the previous highest level. The largest increases in the incidence of measles were 268 in Devonshire, from 871 to 1,139; 232 in Kent, from 1,440 to 1,672; and 196 in Essex, from 1,632 to 1,828; and the largest decreases were 291 in Derbyshire, from 1,046 to 755; and 202 in Yorkshire West Riding, from 2,069 to 1,867. The decrease in the incidence of whooping-cough was mainly contributed by two counties, Yorkshire West Riding with a fall of 117, from 278 to 161, and Lancashire with a decrease of 66, from 621 to 555. The number of notifications of scarlet fever, 1,515, was 30 less than in the preceding week, and no large fluctuations occurred in the local trends. 24 cases of diphtheria were notified, 8 more than in the previous week; the chief feature of the returns was the rise in Lancashire from 1 to 9.

Notifications of paratyphoid fever numbered 6, 9 fewer than in the preceding week. The decreased incidence was mainly due to the experience of Wales, where the cases fell from 11 to 2.

17 cases of acute poliomyelitis were notified during the week. These cases were 5 fewer for paralytic and 4 fewer for non-paralytic cases than in the preceding week. Birmingham C.B. with 2 notifications was the only area with more than one case.

320 cases of dysentery, a rise of 34, were reported. The chief centres of infection were Lancashire 91 (Liverpool C.B. 32, Manchester C.B. 17, Preston R.D. 13), Lincolnshire 39 (Grimsby C.B. 38), London 36 (Wandsworth 9), Essex 34 (Southend-on-Sea C.B. 17, East Ham C.B. 13), and Yorkshire West Riding 27 (Bradford C.B. 14).

530 deaths were registered from influenza in the great towns; these were 84 more than in the preceding week. The rise in mortality occurred in the northern section of the country, while in the southern section it remained constant. The deaths in London and the south-east formed 52% of the total, compared with 61% and 64% in the two preceding weeks.

Industrial Accidents and Disease

The number of work-people (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in January was 100, compared with 137 in the previous month and 130 (revised figure) in January, 1952. The number of cases of industrial disease reported was 30, including 9 from lead poisoning, 3 from anthrax, 10 from epitheliomatous ulceration, and

6 from chrome ulceration. One death due to anthrax from wool was reported.—*Ministry of Labour Gazette*, February, 1953.

Week Ending February 21

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,550, whooping-cough 2,197, diphtheria 16, measles 32,890, acute poliomyelitis 27, dysentery 241, paratyphoid fever 4, and typhoid fever 8.

Medical News

The Diagnosis of Cancer.—The British Empire Cancer Campaign is sending a pamphlet called "The Early Diagnosis of Cancer" to all general practitioners in Britain. The pamphlet describes shortly the chief ways that cancer can present in the various parts of the body and stresses the diagnostic difficulties. Its object is to aid early diagnosis. Accompanying the pamphlet is a letter asking for the doctor's view on the desirability of direct instruction of the lay public on cancer. The letter says that "the Campaign is firmly of the opinion that no steps should be taken in the field of public instruction without the support of the medical profession as a whole." Doctors are asked to give a "yes" or "no" reply on this point.

"B.P., 1953."—The *British Pharmacopoeia, 1953*, which becomes official on September 1, has just been published. It has been completely revised. There are 64 new monographs, and 150 outdated ones have been deleted. The last edition was in 1948, with an addendum in 1951. The most outstanding change is the use of English instead of Latin for the main title of the monographs, which has necessitated a new alphabetical order. The metric system, being that normally used for chemical and pharmaceutical processes, is adopted throughout, although where dosage has been by custom in Imperial units these are also given. The *B.P.* is published under the direction of the General Medical Council. It costs 50s. net.

Nuffield Gerontological Research Fellowship.—The Nuffield Foundation, as part of its programme for the care of old people, is prepared to offer a Nuffield Research Fellowship, of professorial status, for research on the scientific aspects of ageing, or alternatively one or more fellowships of less senior status. Applications for both types of fellowship are invited, and appointment will be made by a committee representing the Royal Society and the Nuffield Foundation. The fellowship, which may be tenable at any university in the United Kingdom, will be open to applicants of either sex—usually not more than 45 years of age—who are of high merit and whose ability fits them for the conduct of original scientific research. Appointment to the senior award will normally be made for a period of five years and may be renewed for further periods of five years. The value will not be less than £2,000 per annum plus superannuation and child allowance. Research expenses will be met by the Foundation, including such provision for research assistants, apparatus, and technicians as the committee may think appropriate. In the event of one or more less senior workers, instead of one senior, being appointed, the period of appointment will be three years in the first instance. The value will be £1,000 to £1,500 per annum plus superannuation, child allowance, and research expenses. Applications must be received before June 1 by the secretary, the Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N.W.1, from whom full particulars and application forms can be obtained.

Psychiatric Research in America.—The creation of a large fund for research in psychiatry was announced last week by the president of Yale, according to the *New York Times*. The fund consists of a grant of $6m. provided by the Social Research Foundation of New York. The headquarters of the fund will be at Yale, although money from the fund will be available to support studies elsewhere in the United States.

Human Behaviour.—Another large and recent American benefaction for research on human conduct is the Ford Foundation's appropriation of $3.5m. to cover the first six years' programme of a new Centre for Advanced Study in the Behavioral Sciences. The funds will be used principally to permit 50 top-flight scholars and scientists to assemble for study and collaboration at the Centre each year. So far the location of the Centre has not been settled, but a board has been appointed to direct the work. The chairman of the board is the president of the Columbia Broadcasting System.

Société Belge de Droit International Médical.—With Professor René Sand as president a new society has been formed in Brussels to study the medical aspects of international law. The aims of the society, which includes both doctors and lawyers among its members, are: to study international medical law and work for its development; to ensure close collaboration between doctors and lawyers, particularly where international law impinges on medical ethics; to give help with the problems inherent in conventions on human rights, and in general to have regard to the impact of international law on medicine. There is a similar society in France.

Index Ophthalmologicus.—At the XVIIth International Congress of Ophthalmology, New York, 1954, a new edition of the "Indicia" will be issued under the title *Index Ophthalmologicus*, and the Ophthalmological Society has been asked to prepare the section covering Great Britain. Any ophthalmologist who is not a member of the Ophthalmological Society of the United Kingdom or the Faculty of Ophthalmologists, and who wishes to be included in this Index, is asked to send his name and address to the honorary secretary, Ophthalmological Society of the United Kingdom, 45, Lincoln's Inn Fields, London, W.C.2, before March 31.

Register of Chiropodists.—The 1952 *Register of Chiropodists* has now been published, and can be obtained by medical practitioners free on request to the Secretary and Registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London, W.C.1. Chiropodists are classified on a geographical basis, and, besides address and telephone number, information is given on qualifications, hospital appointments, and whether private practice is undertaken.

Health Education.—In a praiseworthy attempt to provide authoritative information to those who are interested in health education in its broadest aspects, the Central Council for Health Education is publishing an "Information Digest" twice yearly. This contains extracts from and abstracts of reports and papers which have a bearing on a particular topic selected by the editors, Dr. A. J. Dalzell-Ward and Miss Priscilla Milton. In the issue dated January, 1953, the main headings of the separate sections are "School Health," "Whooping-cough," "The M.O.H. Reports," "Accidents in the Home," and "Health Education Programmes in Local Authorities." The papers selected for abstraction are not necessarily of very recent publication, but they do give a general view of current thought. The "Information Digest" is at present varityped, but future issues will probably be printed.

Dr. H. B. May, director of the clinical laboratories at the London Hospital, will succeed Dr. A. E. Clark-Kennedy as Dean of the London Hospital Medical College on October 1. Until then he will be Vice-Dean.

Mr. C. J. Cellan-Jones, honorary surgeon to the Swansea General Hospital, has been appointed a Deputy Lieutenant of Glamorgan.

Dr. Ludwig Guttmann, director of the Ministry of Pensions Spinal Injuries Centre at Aylesbury, has been invited

to speak at a three-day symposium on stress which is being held from March 16 to 18 at the Army Medical Service Graduate School in Washington, D.C.

Emergency Bed Service: Applications and Admissions.—During the seven days ending March 2 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,302, of whom 86.5% were admitted. The white warning was cancelled from March 3.

COMING EVENTS

Institute of Psychiatry.—Details of the lectures to be given to postgraduate students in psychiatry at the Maudsley Hospital during the term beginning on April 13 are now available from the secretary of the Institute, Maudsley Hospital, London, S.E.5.

Ergonomics Research Society.—The third annual conference of the Ergonomics Research Society will be held at the Department of Human Anatomy, Oxford University, from April 13 to 16. The Chairman of the conference will be Professor W. E. Le Gros Clark, F.R.S., and the main subject for discussion will be "Human Performance: Its Measurement and Limitations." Those wishing to enrol as members of the symposium are asked to communicate with H. Murrell, Spinneys, Marlpit Lane, Headless Cross, near Redditch, Worcs.

Research on Micro-organisms.—The first Marjory Stephenson Memorial Lecture will be given by Dr. D. D. Woods, F.R.S., at the Royal Institution, Albemarle Street, London, at 6 p.m. on April 13. The title will be "The Integration of Research on the Nutrition and Metabolism of Micro-organisms," and all those interested are invited to attend. The Marjory Stephenson Memorial Fund is administered by the Society for General Microbiology.

NEW ISSUES

Abstracts of World Medicine.—The next issue (Vol. 13, No. 3) will be available in a week's time. The contents include abstracts of papers selected from the medical literature of the world on all aspects of clinical medicine and surgery and the allied sciences.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; a specimen will be sent free on request. Obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

Details in this column are necessarily brief. Further information and tickets where required (marked ●) should be obtained from the institution concerned.

Monday, March 9

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At University New Buildings, 5 p.m., Dr. Pierre Mallet-Guy (Lyons): Manometric and Radiographic Control of Biliary Surgery.

INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. E. Stengel: lecture-demonstration for postgraduates.

LONDON UNIVERSITY.—At Bedford College, 5.15 p.m., Professor S. Bergström (Lund): Intestinal Absorption of Fats.

MEDICAL SOCIETY OF LONDON.—8.30 p.m., Lettsomian Lecture by Dr. E. R. Callinan: Some Disorders of the Liver and Bile Passages.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.—7.30 p.m., Professor J. H. Burn, F.R.S.: Progress in Biological Standardization.

Tuesday, March 10

CHELSEA CLINICAL SOCIETY.—At South Kensington Hotel, 8.30 p.m., discussion to be opened by Mr. W. V. Gibson and Sir Hugh Griffiths: Medical Aspects of Road Accidents.

EDINBURGH UNIVERSITY.—At University New Buildings, 5 p.m., Professor A. Meyer: Anatomical Aspects of Neurosurgery in Mental Disorder.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. G. Cochrane: Leprosy.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Oliver-Sharpey Lecture by Dr. Clifford Wilson: Renal Factors in the Production of Hypertension.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Dr. T. Rowland Hill: neurological demonstration.

Wednesday, March 11

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. G. Cochrane: Histopathology of Leprosy.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, W.C., 4.30 for 5 p.m., Dr. A. H. Harkness: Non-gonococcal Urethritis.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8.30 p.m., annual general meeting. Presidential address by Miss Diana Beck: Management of Head Injuries in General Practice

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Erasmus Wilson Demonstration by Mr. V. E. Negus: Protection of the Respiratory Tract. (On the Evidence of Comparative Anatomy.)

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. W. C. Harvey: Food Hygiene.

Thursday, March 12

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Drs. Donald Blair, A. R. Redfern, and E. Weissmann: Three Difficult Cases Treated by Adlerian Methods.

●INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. R. E. Hope Simpson: Epidemiological Research in Children under 15 Years of Age.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Mycology—Pathology of Mycotic Infections.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. J. G. Benstead: Antarctic Observations of Comparative Interest in Hygiene and Forensic Medicine; Dr. A. A. Miller: Case of Concomitant Endometrial Adenocarcinoma with Squamous Metaplasia and Endometrial and Tubal Tuberculosis.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Dorchester Hotel, 6.30 p.m. to 1 a.m., annual dinner-dance.

LONDON UNIVERSITY.—At Bedford College, 5.15 p.m., Professor S. Bergström (Lund): Formation and Interconversion of Bile Acids.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Mr. R. Llewelyn Davies, M.A., A.R.I.B.A.: Modern Trends in Hospital Architecture.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Oliver-Sharpey Lecture by Dr. Clifford Wilson: Renal Factors in the Production of Hypertension.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor J. B. Wyman: The Use of Pentamethonium and Hexamethonium Salts in Major Surgery.

ROYAL SOCIETY.—11 a.m., discussion to be opened by Professor J. Z. Young, F.R.S.: Function and Location of Enzymes in Cells.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Sir James Spence: Methods of Clinical Teaching.

UNIVERSITY COLLEGE.—At Physiology Theatre, 4.45 p.m., public lecture by Professor V. B. Wigglesworth, F.R.S.: Chemical Aspects of Insect Physiology.

Friday, March 13

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. R. G. Cochrane: Leprosy.

OXFORD UNIVERSITY.—At Department of Human Anatomy, 12 noon, Professor G. W. Corner (Washington): Application of Scientific Methods to the Study of Sex and Reproduction.

Saturday, March 14

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Hull Royal Infirmary, 2 p.m., meeting.

APPOINTMENTS

BLACK, DORIS JEAN, M.B., B.Ch., Assistant Divisional Medical Officer to the Chorley, Adlington, and Coppull areas of Division 4, Lancashire County Council.

CULLINGTON, D. E., M.B., B.Chir., D.P.H., D.C.H., Medical Officer of Health, Barking, and Area Medical Officer and Divisional School Medical Officer.

DAVIES, J. B. M., M.D., D.P.H., Deputy Medical Officer of Health and Deputy Port Medical Officer, City of Liverpool.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Catherine N. McRobert, M.B., B.S., Resident Medical Officer at Tadworth Court; Ruth E. Trilling, B.M., B.Ch., D.C.H., Assistant Resident Medical Officer at Tadworth Court.

MORRIS, NORMAN F., M.D., M.R.C.O.G., First Assistant in Obstetric Unit, University College Hospital, London, W.C.

RAFTERY, J. D., D.Phil. F.R.C.S., Visiting Senior Orthopaedic Surgeon to King Edward VIII Hospital, Durban, and Part-time Assistant in the Department of Anatomy, Faculty of Medicine, University of Natal, Durban, South Africa.

VICKERY, K. O. A., M.D., D.P.H., Medical Officer of Health and School Medical Officer, County Borough of Eastbourne.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Evershed.—On February 5, 1953, at the Liverpool Maternity Hospital, to Elizabeth, wife of Squadron Leader T. A. Evershed, M.B., B.Chir., R.A.F., a son.

Heller.—On February 19, 1953, at St. Mary's Hospital, London, W., to Betty, wife of Dr. Michael Heller, a son—Simon Richard.

Solomon.—On February 9, 1953, at the Bearsted Memorial Hospital, London, N., to Vera (formerly Apt), wife of Dr. Terence Solomon, M.B., D.Obst.R.C.O.G., a son—Stephen Maxwell Ernest.

Walwyn-Jones.—On February 24, 1953, to Margaret (formerly Pemberton), wife of Dr. E. O. Walwyn-Jones, a son.

Winter.—On February 28, 1953, at the Gordon Road Nursing Home, Cardiff, to Mollie, wife of George Winter, M.B., Ch.B., a sister for John.

DEATHS

Joscelyne.—On February 11, 1953, Edward Walter Joscelyne, M.D., of 13, Stoke Grove, Westbury-on-Trym.

Kerr.—On February 10, 1953, at Grimsby, James Arthur Kerr, V.R.D., M.D., D.P.H., Surgeon Commander, R.N.V.R., aged 54.

Pickard.—On February 9, 1953, at Rustholme, Streatham Drive, Exeter Ransom Pickard, C.B., C.M.G., M.D., M.S., F.R.C.S., Colonel, A.M.S., T.A., retired, aged 85.

Reid.—On February 10, 1953, at Walsall, Gordon Campbell Kinloch Reid, M.B., Ch.B.

Shears.—On February 5, 1953, at Beckenham Hospital, William Shears, late of Bromley Road, Catford, S.E., and 1, North Dene, Beckenham, Kent, aged 84.

Smith.—On February 13, 1953, at his home, Rodborough Grange, Alyth Road, Bournemouth, Hants, Alfred Tennyson Smith, O.B.E., M.D., aged 83.

Stewart.—On February 8, 1953, at Olney, Sandy Lane, St. Paul's Cray, Kent, Ian James Allan Stewart, M.B., Ch.B., aged 50.

Thompson.—On February 13, 1953, at Ashford Hospital, Hubert Gordon Thompson, M.D., F.R.C.S., of "Bennetts," Appledore, Kent, formerly of China, aged 74.

Turner.—On February 9, 1953, Reginald George Turner, C.M.G., D.S.O., F.R.C.S., Colonel I.M.S., retired, of Ardmore Road, Lower Parkstone, Dorset, late of Clevedon, Somerset.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Chilblains in Women

Q.—*Why do women get chilblains more frequently than men?*

A.—It is true that chilblains occur rather more frequently in women than in men, though they chiefly affect children and young adults. The individual predisposition appears to rest upon a vasomotor sensitivity which in turn is subject to emotional and endocrine influences. Over and above these considerations, which would favour an increased susceptibility in the female, is the question of clothing. The body temperature to some extent controls the vascular tone in the extremities, and it is desirable that body and limbs should be maintained at an even and adequate temperature by suitable clothing to prevent perniosis. In the matter of clothing the female is usually more adventurous than the male.

Foot-drop after Delivery

Q.—*I have encountered two cases of foot-drop following delivery, in one of which there was sciatic pain and muscular wasting. It has been suggested that this was due to prolapse of an intervertebral disk. Is this a recognized complication of pregnancy or labour?*

A.—Peroneal palsy is a well-recognized, although fortunately not very common, complication of childbirth. It may be bilateral but is mostly unilateral. The degree of paralysis varies from slight weakness of the dorsiflexors of the foot and toes to inability to move the leg. The affected muscles are flaccid and wasted. Sensory loss is a more variable finding. Sciatic pain and paraesthesiae in the foot may, or may not, be present.

This condition affects primiparae more than multiparae. It may follow normal labour, but seems more common after prolonged labour and difficult forceps deliveries. The first evidence of it may arise during labour or immediately afterwards, but sometimes it is not apparent for several days or weeks. When there is such an interval the injury is probably still attributable to labour, but may have been slight and overlooked. The older and traditional view about its aetiology is that it arises as the result of injury to the lumbosacral cord as it crosses the pelvic brim to join the sacral plexus. The injury is said to arise either by direct pressure of the foetal head or forceps blade, or by traction on the relatively fixed nerve root. A more recent explanation[1] is that the paralysis is the result of a slipped disk—usually the disk between L.5 and S.1. This view has been widely but not universally accepted. Sometimes it is suggested that the mechanism of production may not be the same in all cases.

The prognosis is good in that the muscular wasting and weakness nearly always clears up in time—although it may take many months: it is usually said that recovery is invariably complete, and it is for all practical purposes. In fact, however, special tests often reveal some weakness in one or more groups of muscles many years afterwards. Moreover, if in after life the subject of such an injury is ever confined to bed for a long period, this weakness shows up temporarily.

If the best result is to be obtained, the management of the case is important and should be in the hands of an orthopaedic specialist. Usually the treatment is the same as for any flaccid paralysis of muscles—massage, galvanic stimulation, and the prevention of stretching of the muscles and permanent deformity by suitable splints or plaster. If there is evidence of disk protrusion it may be necessary to keep the patient at rest in bed for several weeks, and operative treatment might have to be considered in the very severe case. Little can be done to prevent this injury, but if a patient complains of severe sciatic pain during labour it should be regarded as a warning not to proceed with vaginal delivery unless it is reasonably certain that there is no mechanical difficulty at all, and that there will be no need for the application of forceps.

The above comments are based on the assumption that paralysis due to regional analgesia, or to pressure on the peroneal nerve by any appliance used to maintain the lithotomy position, has been excluded.

REFERENCE

[1] O'Connell, J. E. A. (1944). *Surg. Gynec. Obstet.*, 79, 374.

Diagnosis of Polycythaemia Vera

Q.—*What criteria are necessary to establish a diagnosis of polycythaemia vera? Is there any test which will exclude or confirm the presence of the disease beyond question? I have a patient who complains of vertigo, "headiness," "oppressive feelings," and tinnitus, whose R.B.C. count is 6,500,000 (Hb 117%). Are the symptoms likely to be related to the blood picture in this case?*

A.—Polycythaemia requires for its diagnosis a persistently raised erythrocyte count and an increase in the packed cell volume; there is, naturally, an accompanying elevation of the haemoglobin level in most, but not all, instances. The upper limit of normal given by Wintrobe (*Clinical Hematology*, 3rd ed., 1951, Kimpton, London, for the red cell count is 6,200,000 per c.mm. for the male and 5,400,000 per c.mm. for the female, and for the packed cell volume 54% and 47% respectively. Most authorities would agree that red cell counts above 7,000,000 per c.mm. and packed cell volumes above 55% were always abnormal. The next step in diagnosis is the exclusion of such causes of secondary polycythaemia as cyanotic congenital heart disease and emphysema. Given their exclusion, a diagnosis of polycythaemia vera can then be accepted; it is made more certain by the presence of splenic enlargement and by a neutrophil leucocytosis with an increase in the platelet count. These remarks are sufficient to show that there is no single test which alone will "exclude or confirm the presence of the disease beyond question."

In the instance cited, the red blood cell count is perhaps just above the upper limit of normal; the symptoms, although not of specific significance, are those experienced by many polycythaemics; splenomegaly and leucocytosis would suggest that this patient has, in fact, polycythaemia vera. These symptoms are usually to be noted in the older patients and it seems likely that the combination of arterial degeneration with unduly viscid blood is responsible for them.

Prevention of Scale in a Sterilizer

Q.—*What is the best way of preventing the deposition of scale in a sterilizer?*

A.—From the wording of the question it is assumed that the sterilizer is one in which instruments are submerged in boiling water as distinct from their being enveloped in steam.

If this is the case, there are two methods of avoiding the deposition of scale. The more obvious method is to use softened water instead of hard water. At the same time it should be observed that even softened water should be rejected and replaced from time to time, for, with constant re-use and replenishment to make up for evaporation, excessive alkalinity or even a deposit will eventually be encountered. If softened water is not available the trouble can generally be avoided by adding a small quantity—the amount is not critical—of "calgon" (sodium hexametaphosphate) to the water. Here again, periodical rejection and replacement of the water is necessary if it is constantly re-used and topped up.

Crystalline or Procaine Penicillin

Q.—*Which is the better preparation of penicillin for routine parenteral use—crystalline penicillin or a procaine penicillin? I have heard that the likelihood of the side-effects from the procaine in the procaine penicillin outweighs its advantages.*

A.—Arguments about the relative merits of the two preparations are usually based on theoretical considerations rather than on any observed difference in therapeutic potency. After an intramuscular injection of 600,000 units of procaine penicillin a bacteriostatic level in the blood is maintained for 24 hours as a rule, whereas after an injection of the same dose of crystalline penicillin the concentration in the blood rises to a much higher peak, but rapidly declines to a level which is too low to be assayed. The ability of procaine penicillin to maintain a significant blood-concentration over a prolonged period would suggest that it was the preparation of choice for prophylactic use—for example, as a protective screen for the patient with valvular disease of the heart who requires dental extraction. On the other hand, in the treatment of established infections the high initial concentration of penicillin in the blood achieved with the crystalline salt may facilitate penetration of the antibiotic into the diseased tissues, where high concentrations may be found many hours after the blood level has fallen to zero. In practice the injection of 500,000 units of crystalline penicillin twice a day gives satisfactory therapeutic results. Reports of alarming, even fatal, responses to the administration of procaine penicillin (probably due to inadvertent intravenous injection) should be viewed against the background of the millions of injections that have been given without mishap; the incidence of dangerous side-effects is far too low to justify condemnation of procaine penicillin on this score.

Papaverine

Q.—*What are the actions of papaverine? Is it useful clinically in the treatment of disorders such as angina pectoris and essential hypertension? If so, please indicate dosage.*

A.—Papaverine is a feebly analgesic and narcotic alkaloid of opium which has a relaxing action on smooth muscle. The official preparation is papaverine hydrochloride, but it is also available as a sulphate and a nitrite. The usual dose is from 0.12 to 0.25 g. orally, but there are reports of as much as 1 g. being given intravenously without ill effect. Papaverine has been used extensively, especially on the Continent, in the treatment of angina, hypertension, and peripheral vascular disorders, but the effect is of short duration and the reports on its use are conflicting. It cannot be said to have any proved value in the treatment of these conditions.

Alcoholic and Traumatic Amnesia

Q.—*Is it possible to differentiate between the amnesias due to head injury and alcoholic excess by the use of thiopentone or methylamphetamine?*

A.—It should be possible to go some way towards clearing up an amnesic gap by investigation under intravenous thiopentone; and in some cases intravenous methylamphetamine might be tried as an alternative, though with much less prospect of success. Ordinary hypnosis will also sometimes succeed. Such measures should be completely successful in an amnesia solely due to hysterical dissociation, unless the patient is uncooperative. But with organically caused amnesias, though some forgotten events may be recalled, an irreducible minimum of amnesia usually remains. In this case it is presumably desired to explore the amnesia as a differential diagnostic method, to decide how far it might be caused by trauma or by alcohol. If the patient was in a deep alcoholic stupor he would be just as unconscious as after a severe concussion. In both cases, therefore, there might be equally good reasons for a permanent and irreducible amnesic gap. The principal prospect of a thiopentone investigation would then be to fill in the story as far as possible, and in the light of a better knowledge of the circumstances so gained it might be possible to decide whether alcohol or trauma was implicated.

NOTES AND COMMENTS

Allergic Rhinitis.—Dr. MORRIS CUTNER and Dr. B. S. SWEETMAN (Chelsea, S.W.3.) write: May we supplement the answer under the above heading ("Any Questions?" February 7, p. 347) by quoting our experience? During the past 18 months or so we have submitted seven patients suffering from this condition to a course of histamine ionization. Of these, three have apparently been cured, two have been markedly improved, one (who incidentally has been relieved of her asthma) has not yet responded favourably, and one did not benefit. The numbers are small, but the clinical impression is significant. The only snag is that as each treatment aims at a general reaction it should (as in our cases) be carried out only by a competent therapist under direct medical supervision. As the patient in question derives some benefit from antihistamine drugs she would very likely benefit by this therapy. We hope to submit an article shortly giving clinical and other reasons for this belief.

OUR EXPERT writes: I have no personal experience of histamine ionization, but zinc ionization will help about half those with allergic rhinitis.

Night Starts.—ANOTHER DOCTOR writes: I was interested to read your correspondent's account of night starts in his legs following transverse myelitis (February 14, p. 414). I too have a spastic paralysis of both legs from a transverse myelitis. I observe that the degree of spasticity in my legs varies with the state of my large bowel. If I allow myself to become constipated the legs become much worse: if, on the other hand, the bowel is irritated with too much laxative the spasticity increases also. There is no doubt in my mind that these "kickings" of the legs are the result of an incoordination of large bowel peristalsis causing localized sections of the bowel to become dilated with flatus, and that they are motivated through a spinal reflex arc, the inhibitory impulses of the cerebral cortex having been cut off by the pyramidal lesion at the level of the myelitis. It is probable that air-swallowing during sleep is a factor in producing pockets of gas in the incoordinated large bowel. If I avoid flatus-forming foods the severity of the spasticity diminishes and vice versa. Weather conditions also have a very noticeable effect on the spasticity and "kicks," and it may well be that the lowering of the atmospheric pressure produces increased intra-abdominal pressure from the expansion of the flatus contained in the bowel.

Corrections.—In the obituary notice of Dr. Harold Balme (*Journal*, February 28, p. 511) we mistakenly recorded that he had only one son. In addition to Mr. David Mowbray Balme, Principal of the University College of the Gold Coast, Dr. Balme had another son, Dr. Harold Wykeham Balme, and two daughters.

In the appreciation of the late Sir William Douglas in last week's *Journal* (p. 513) he was wrongly described as Parliamentary Secretary to the Ministry of Health. Sir William's post was that of Permanent Secretary.

Dr. M. H. ARMSTRONG DAVISON writes: At the recent R.S.M. meeting on "Hypotension in Anaesthesia" (see February 28, p. 504), I stated that there had been only one death "on the table" in the last 60,000 anaesthetics given at the Royal Victoria Infirmary, Newcastle-upon-Tyne. I have subsequently discovered that there were in fact two such deaths.

The dose of L-thyroxine given in the second paragraph of the summary of the paper by Russell Fraser and M. Wilkinson in our issue of February 28 (p. 484) should read 0.1 mg. thrice daily, and not 1 mg.

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